VALVULAR HEART DISEASES

Case: A 55-year-old male presented with dyspnoea on exertion, palpitations and nocturnal angina symptoms. On examination- Bisferiens pulse and Early diastolic murmur at left 3rd ICS noted. What's your diagnosis?

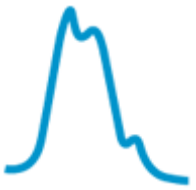
Symptoms

- **Haemoptysis:** MS (M/C Source- Bronchial Vein)
- **Nocturnal Angina:** AR
- **Fatigue:** MR
- **Syncope:** AS

Pulse

- **Bisferiens pulse:** Seen in AR

  Two peaks felt between S1 and S2. Highly characteristic of **Aortic Regurgitation.**



- **Parvus et Tardus:** Low amplitude, late peaking
  Indicates obstruction to ventricular outflow

  Suggestive of **Aortic Stenosis**

Murmurs

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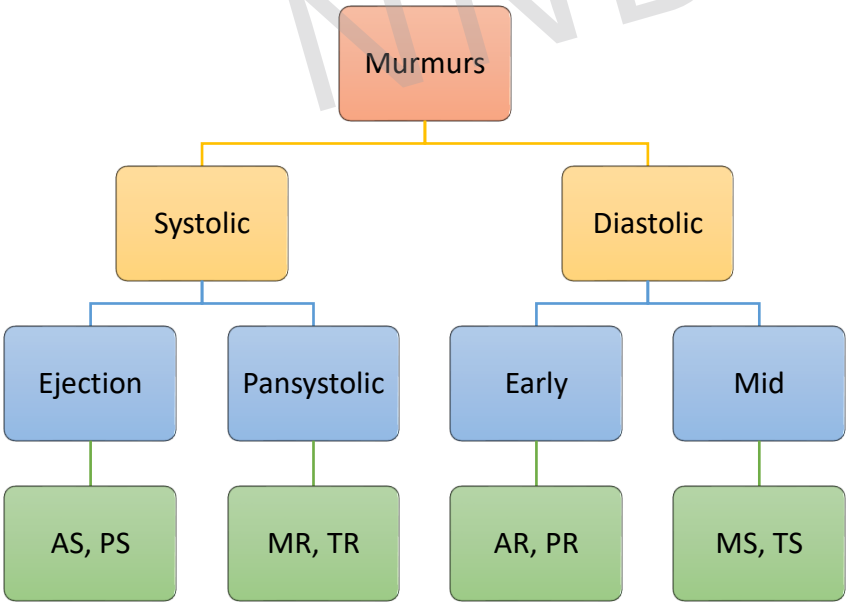

- **Ejection Systolic:** Blood going from ventricles to the blood vessels.
  The turbulence will be after the semilunar valve open and usually peaks in the mid systole and then decreases in intensity (Crescendo Decrescendo Murmur a/k/a mid-diastolic murmur)

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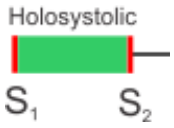
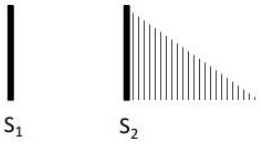
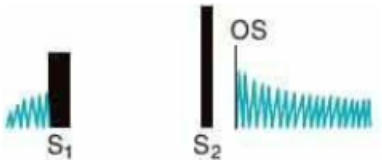
- **Pansystolic:** Can be heard uniformly throught the systole. (a/k/a Holosystolic murmur)



- **Early Diastolic:** Only seen in regurgitation of semilunar valves.
  Primary murmur of AR is k/a Key Hodgkin's Murmur
  Primary murmur of PR is k/a Graham Steel Murmur



- **Mid diastolic:** Start after the opening of AV valves.
  Then shows a decreasing trend. And then at last shows a 'presystolic accentuation'.



Causes of various valvular heart defects

Right Sided

1. **TS** – Rheumatic Heart Disease (RHD)
2. **TR**- RV dilatation (When RV Dilates, the distance between the leaflets of the tricuspid valve increases resulting in the regurgitation. This RV Dilatation may be due to underlying causes such as *Cor pulmonale* or *Pulmonary Embolism*)
3. **PS**- Congenital causes
4. **PR**- Pulmonary Artery HTN

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Left Sided

1. **MS**- RHD
2. **MR**- RHD (Most Common cause of MR overall is RHD, in western population it is Mitral Valve Prolapse)
3. **AS-** Calcification
4. **AR-** Age related Degeneration

- Carcinoid Syndrome-Produces SEROTONIN which degrades into the lungs. Therefore, it affects only the right side of the heart and is degraded before it can reach the left side. Therefore, the most common CVS Lesion due to carcinoid syndrome is Tricuspid Regurgitation- TR.

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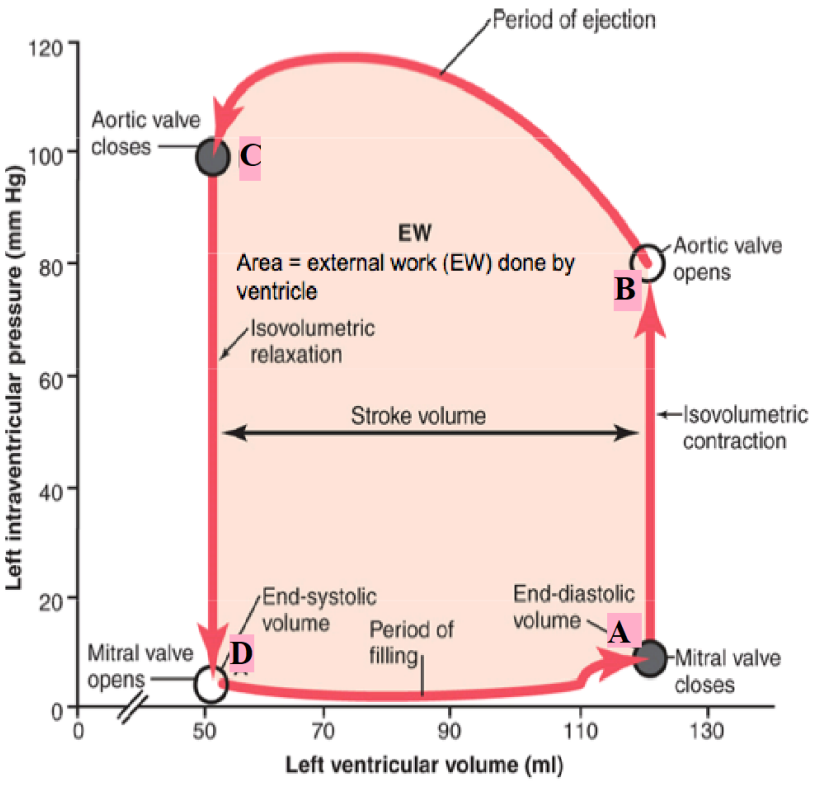
Physiology

Left ventricular pressure-volume loop



- **Point A:**
  - End of Diastole
  - LV Volume: 120 ml (Max Vol)
  - LV Pressure (LVP): 5-10 mm Hg
  - Mitral valve closes because the LVP>LA Pressure; giving rise to S1.

- **A to B- Isovolumetric Contraction**
  - Mitral Valve: Closed
  - Atrial Valve: Not yet open
  - The LV contracts as a closed chamber.
  - Rapid Rise of LVP without any change in the volume
  - Till LVP reaches 80 mm of Hg

- **Point B**
  - LVP exceeds the diastolic pressure in Aorta, and the Aortic Valve opens.
  - Opening of valve does not produce any sounds.

- **B to C- Period of Ejection**
  - Constitutes two phases- Rapid & Slow Ejection phase (Cant be distinguished graphically)
  - During Rapid Ejection Phase- the LVP rises rapidly and the LV Volume drops rapidly.
  - During the Slow Ejection Phase- The LVP starts to decrease due to mostly empty LV.

- **Point C**
  - As the LVP < Aortic Pressure, the Aortic Valves close down, producing S2.
  - Marks the end of Systole

- **C to D- Isovolumetric Relaxation**
  - The LV relaxes while being a closed chamber
  - LVP further decreases

- **Point D**
  - As the LVP < LA Pressure, the Mitral valve open up.

- ✓ **D to A – Period of Filling**
  - Blood passively fills up the LV.
  - Massive increase in LV Volume without any significant increase in the LVP, because the ventricles are compliant structures.

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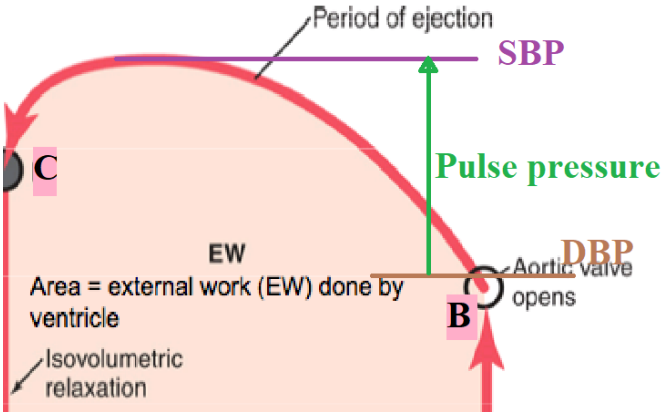
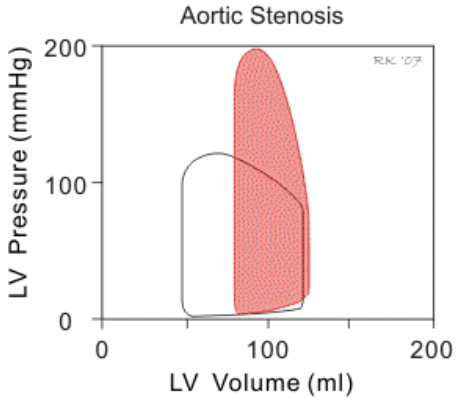
- ✓ **The width of the curve:** denotes the **Stroke Volume**
- ✓ Ejection Fraction = Stroke Volume / End Diastolic Volume
- ✓ **Blood Pressure estimation:**



LV Pressure Volume Loops in Valvular Heart Diseases



- **Tall and Narrow Loop**
  - Stroke Volume decrease
  - Indicates Stenotic lesion
  - Tall: LV has to exert an extra pressure to open the stenosed valve
  - Classically seen in **AS**

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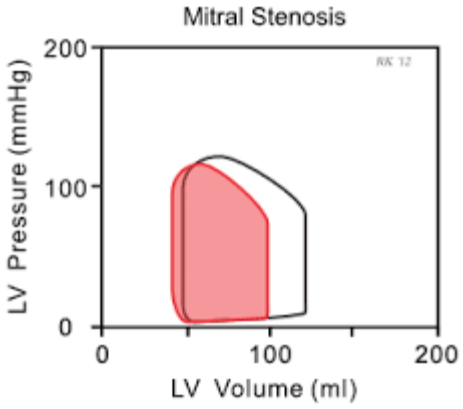
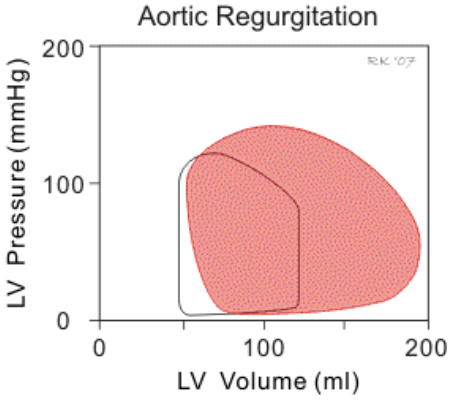


- **Shift of Loop to LEFT**
  - Narrower Loop
  - Indicates stenosis
  - Decrease in End Diastolic Volume
  - LV in not getting properly filled.
  - Seen in **MS**



- **Broad Loop**
  - Stroke Volume has increased
  - Indicates Regurgitant lesion
  - Isovolumetric relaxation phase is NOT a straight line but is slanting towards right. Indicates change in volume of LV during isovolumetric relaxation.
  - Huge increase in End diastolic volume
  - Seen in **AR**

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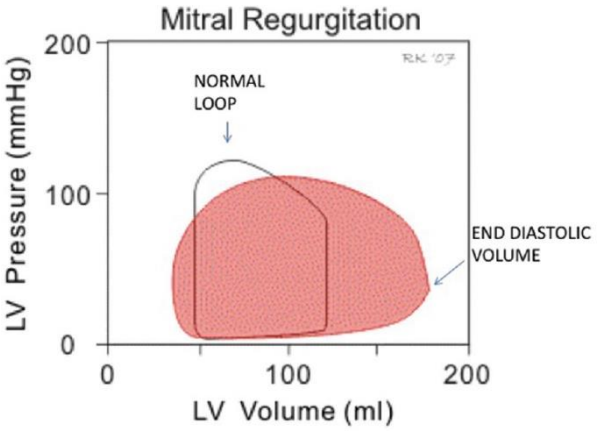
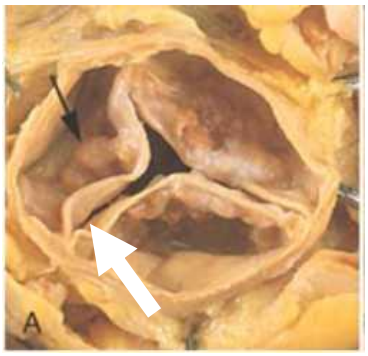
- **Broad Loop**
  - Stroke Volume has increased
  - Indicates Regurgitant lesion
  - Isovolumetric relaxation phase is NOT a straight line but is a curve. First a decrease in LV Volume and then an increase.
  - This is due to regurgitation of blood from LV to LA during this phase, and later coming back to LV Volume
  - Seen in **MR**



Pathologies of Valvular Heart Diseases

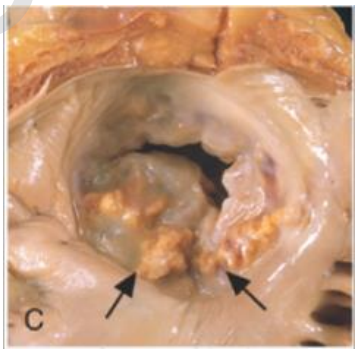
1. Calcified Aortic Valvular Stenosis

- Cusps involved
- Metaplastic bone formation
- No commissural fusion (White Arrow)



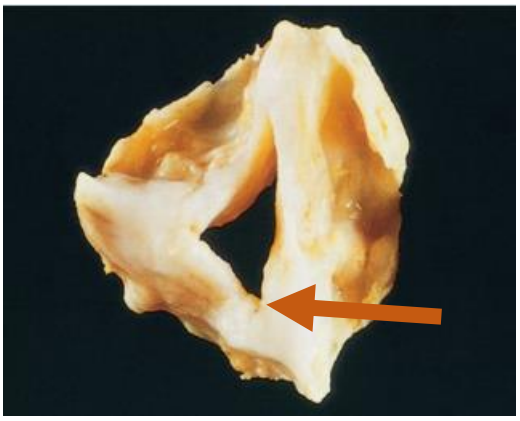
2. Mitral annular calcification

- Cusps NOT involved
- Calcification in annulus
- No commissural fusion



3. Rheumatic aortic stenosis

- Commissural fusion present



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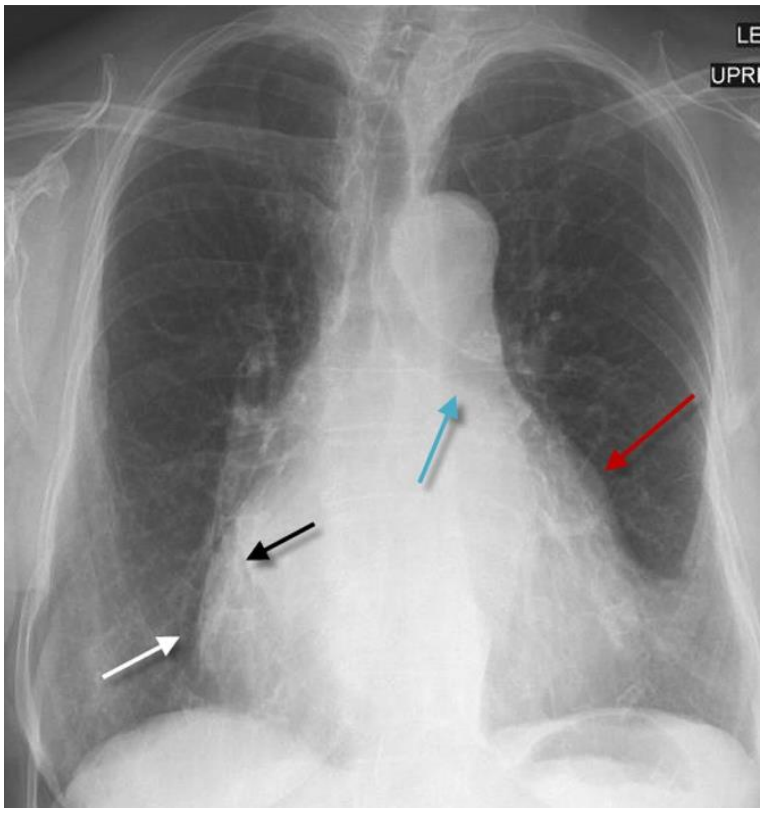
Chest XRay – MITRAL STENOSIS

XRAY features due to RISE in LA Pressure

- *Earliest*- Bulge in Left Auricle (Red Arrow) a/k/a Straightening of the Cardiac border Or **Third Mogul Sign**
- Carinal Angle is widened and Left Main Bronchus is lifted up (Blue Arrow)
- Double Atrial Shadow
  - RA Shadow (White Arrow)
  - LA Shadow (Black Arrow)



ECG Findings

1. MITRAL STENOSIS

Sequence of events: **LA Enlargement** → Pulm HTN → **LV Hypertrophy**→ **RA Enlarges**

a) LA Enlargement:

Lead V1- Enlarged P wave (MORRIS Index positive)

b) LV Hypertrophy:

Lead V1- QRS will be positive (Normally it's overall negative in V1)

R wave > 7 mm

c) RA Enlargement:

Lead II – P wave >2.5 mm

2. MITRAL REGURGITATION

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Sequence of events: **LA Enlargement → LV Hypertrophy**

- For LV hypertrophy:

  LEAD V5 or V6 - Increased R wave height (>25mm)

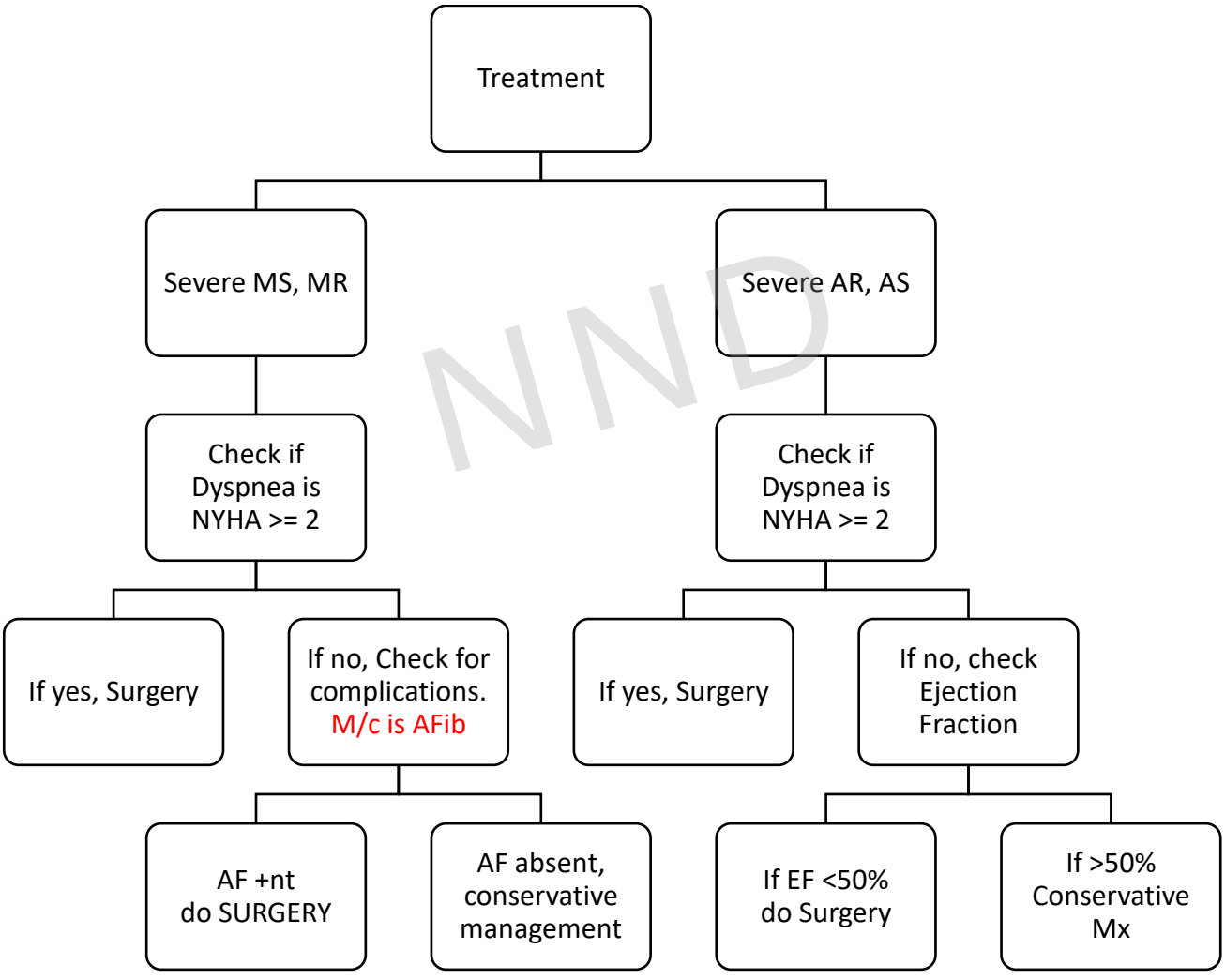
  But

  - If due to Volume Overload – ST segment and T waves will be normal in V5 and V6. Eg- MR/AR

  - If due to Pressure Overload – ST segment depression and T waves inversion in V5 and V6 (Strain Pattern) Eg- AS

TREATMENT

- **Severe MS-** Mitral Valve area of <1.5 sq.cm on echocardiography
- **Severe MR-** Regurgitant Jet of >60ml/beat on echocardiography
- **Severe AS-** Aortic Valve area of <1 sq.cm on echocardiography
- **Severe AR-** Regurgitant Jet of >60ml/beat on echocardiography


Treatment
Severe MS, MR
Severe AR, AS
Check if Dyspnea is NYHA >= 2
Check if Dyspnea is NYHA >= 2
If yes, Surgery
If no, Check for complications. M/c is AFib
If yes, Surgery
If no, check Ejection Fraction
AF +nt do SURGERY
AF absent, conservative management
If EF <50% do Surgery
If >50% Conservative Mx

Surgery of Choice:

- MS: Balloon Valvotomy
- MR: Valve Replacement/Repair

Rheumatic Fever

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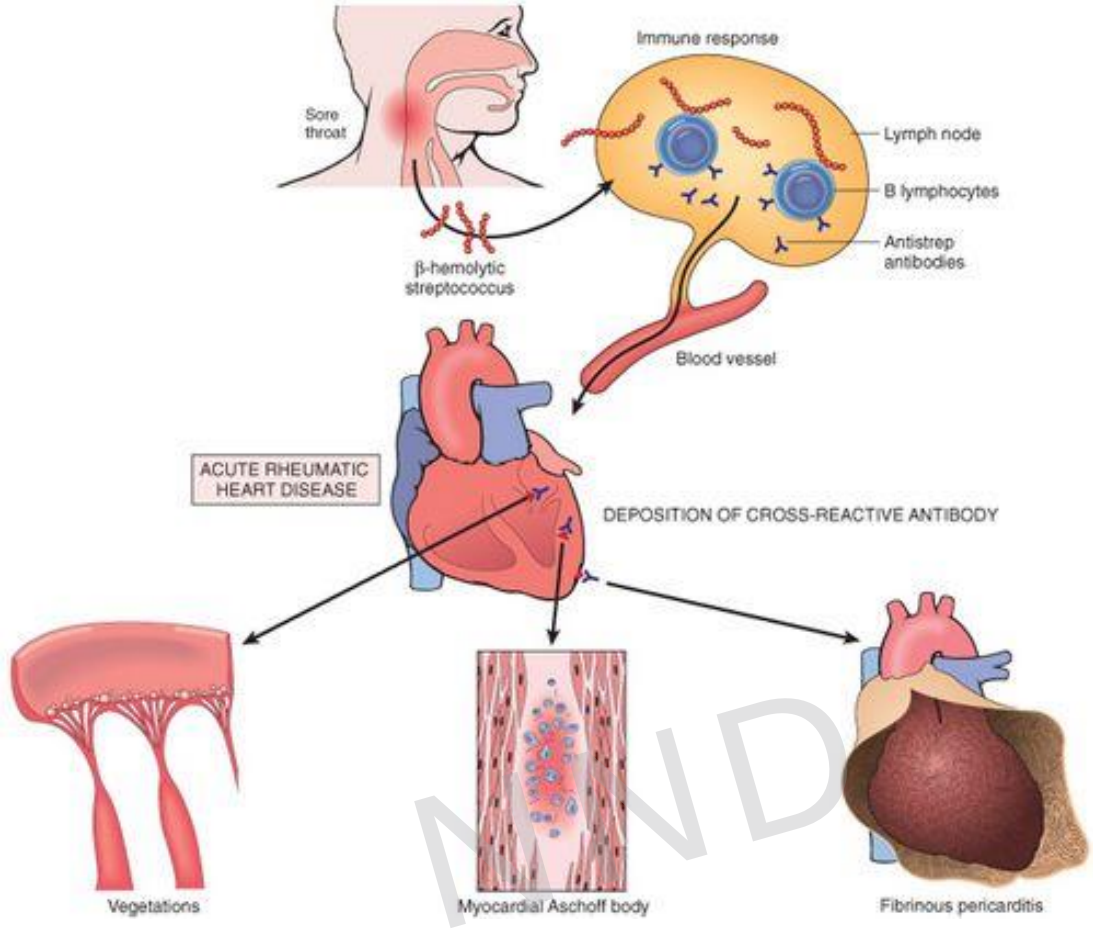
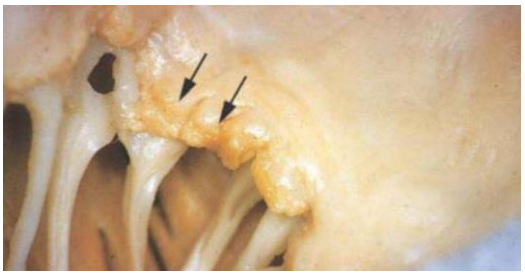
Case: A 21-year-old young man presents in emergency with high grade fever with inflammation of knee and ankle joints which is fleeting in nature. There is history of occasional palpitations. There is history of antecedent sore throat. The ECG shows prolongation of PR Interval. What's the most likely diagnosis?

Pathogenesis of Acute Rheumatic Fever



- Type 2 Hypersensitivity
- Anti-streptococcal antibodies attack myocardium due to cross reactivity.
- Develops cardiac valvular manifestations.
- Fibrinous pericarditis a/k/a Bread and Butter pericarditis.



- Rheumatic Vegetations: Irregular, small warty vegetations, along the line of closure of the valve.

- Microscopy: Aschoff Nodules (granulomas)

*Anitchkov cells a/k/a caterpillar cells.

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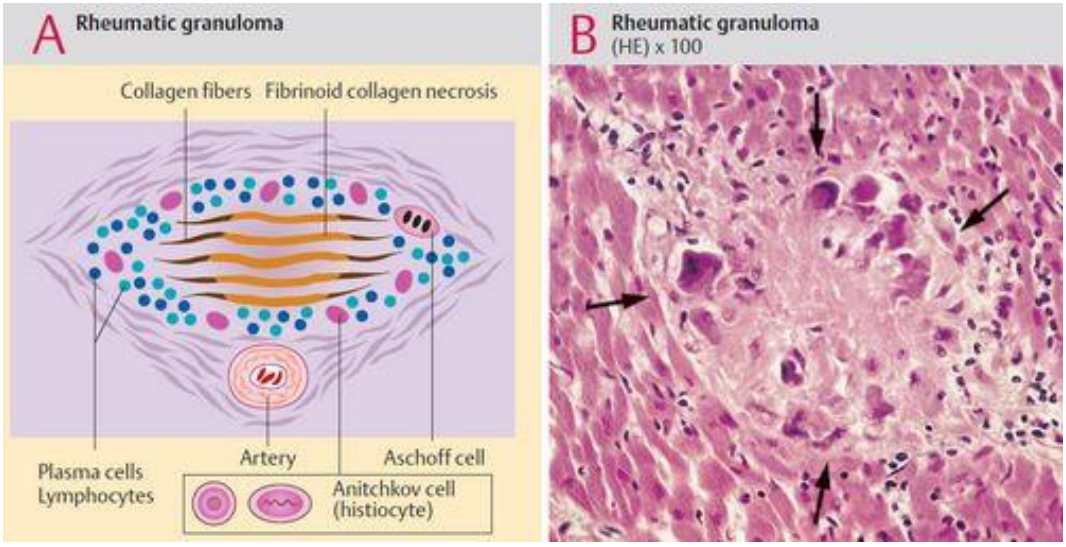

Treatment for manifestations

1. Arthritis: Aspirin
2. Carditis: Diuretics, Steroids (Refractory carditis), Valve replacement (Last option)
3. Sydenham Chorea: **Sedation**, Antiepileptic- Valproate, IVIG (Refractory Chorea)

"If Arthritis features do not get better within 24 hours of aspirin administration, you can safely rule out a rheumatic cause for Arthritis"

Prophylaxis

1. **Primary prophylaxis:** Patient has developed sore throat, prevent development of Acute Rheumatic Fever

Rx. Antibiotic within 9 days from onset of symptom
Single Dose Benzathine Penicillin or
Azithromycin, if penicillin allergic

2. **Secondary Prophylaxis:** Single episode of ARF has occurred. Prevention of recurrent episodes.

a) **No Carditis-** Benzathine Penicillin x 3 weekly till 5 years or till patient age is 21 years, whichever is longer.
b) **Carditis**- Benzathine Penicillin x 3 weekly till 10 years or till patient age is 21 years, whichever is longer.
c) **Already RHD**- Benzathine Penicillin x 3 weekly till 10 years or till patient age is 40 years, or lifelong

Infective Endocarditis

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Case: A 30-year-old male k/c/o RHD presented with 3 weeks history of fever and palpitations. Today he presented with sudden onset left sided weakness of left upper and lower limbs. One Examination, finger tips tenderness is present with splenomegaly. Echocardiography shows new regurgitant mitral regurgitation. What is the most likely cause of this presentation?

Clues in the question:

- RHD + Fever → Infective endocarditis (IE)
- Hemiparalysis→Stroke→Sequel of IE
- Osler's Nodes → IE
- MR

ENDOCARDITIS

Duke Criteria

IMIG

MAJOR CRITERIA

Persistently +ve blood culture for typical organisms

ECHO: vegetation, dehiscence, abscess

New valvular regurgitation murmur

Coxiella burnetii infection

MINOR CRITERIA

Predisposing heart condition or IV drug use

Fever - 38.0°C

Vascular: emboli to organs / brain, hemorhages

Immunologic: glomerulonephritis, Osler's nodes, Roth spots, rheumatoid factor

Positive blood cultures that do not meet specific criteria

DEFINITE ENDOCARDITIS

2 major clinical criteria

1 major & any 3 minor clinical criteria

5 minor clinical criteria

Histological findings

+ve Gram stain or cultures from surgery or autopsy

POSSIBLE ENDOCARDITIS

1 major and >1 minor clinical criteria

3 minor clinical criteria

REJECTED ENDOCARDITIS

Resolution within <4 days of Abx

Alternate diagnosis is made

No evidence of IE found at surgery or autopsy (after antibiotic therapy for ≤4 days)

Definite or possible criteria not met

- Predisposing Factors:
  - Most Common Heart disease- RHD
  - Most Common Valvular Heart Ds- MR
  - Most Common CVS Factor- IV Drug Abuse

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Infective Endocarditis: *Pathogenesis, complications, and clinical findings*

Poor dental hygiene/ recent dental procedure

Intravenous drug use *(mostly cause R sided endocarditis)*

Invasive procedure/ indwelling device

If no Bacteremia- causes NON BACTERIAL THROMBOTIC ENDOCARDITIS (NTBE)

In acute endocarditis, valve trauma or the invading bacterium damages the valve endothelium

In subacute endocarditis, non laminar flow (due to pre-existing valvular stenosis or regurgitation) damages valve endothelium, a sterile thrombus forms

Bacteria (*see Microbiology Note*) enter the bloodstream (**Bacteremia**)

- **Positive blood cultures**
- *Activation of immune system → generalized immune response* → **Fever, Malaise**

Thrombus forms on the surface of a cardiac valve → Bacteria adhere to thrombi on the cardiac valve endothelium

Infection of the thrombus typically produces a vegetation on the flow surface of a valve.

- *In subacute cases, valvular abnormality usually present beforehand* → **Mitral Regurgitation, Aortic Stenosis, Aortic Insufficiency** (Valve Involvement: Mitral > Aortic > Tricuspid)
- *In all cases, vegetation forms on affected valve* → **Vegetation seen on ultrasound** (echocardiogram)

Formation of immune complexes (complexes of antibody bound to antigen) secondary to infection

- *Immune complexes deposit in kidney → damage to glomeruli* → **Glomerulonephritis**
- *Immune complexes cause vasculitis in retinal vessels* → **Roth's Spots** (retinal hemorrhages with pale centers due to coagulated fibrin)
- *Immune complexes deposit subcutaneously* → **Osler Nodes** (*tender*, raised, red lesions found on the hands & feet)

Parts of vegetation embolize systemically, obstructing arteries

- *↓ blood flow to organs perfused by the obstructed arteries* → **Organ infarction**
- *Smaller emboli block smaller vessels on hands/ feet → microinfarctions*
  - **Splinter hemorrhages** (small red streaks under nails)
  - **Janeway Lesions** (non-tender, red macules/ nodules on palms/soles – only a few milimeters wide)

Infection destroys infected valve → *Valve unable to fulfill normal functions* → **Cardiac valve insufficiency, regurgitation**

Microbiology Note:
bacteria causing endocarditis varies depending on the type of valve:

- **Native Valve:** *Viridans streptococci* (in young patients), *Enterococcus* (in older patients), *Staph aureus* (for both)
- **Prosthetic Valve:** *Staph aureus* or Coagulase-negative *Staph*

Legend: Pathophysiology | Mechanism | Sign/Symptom/Lab Finding | Complications

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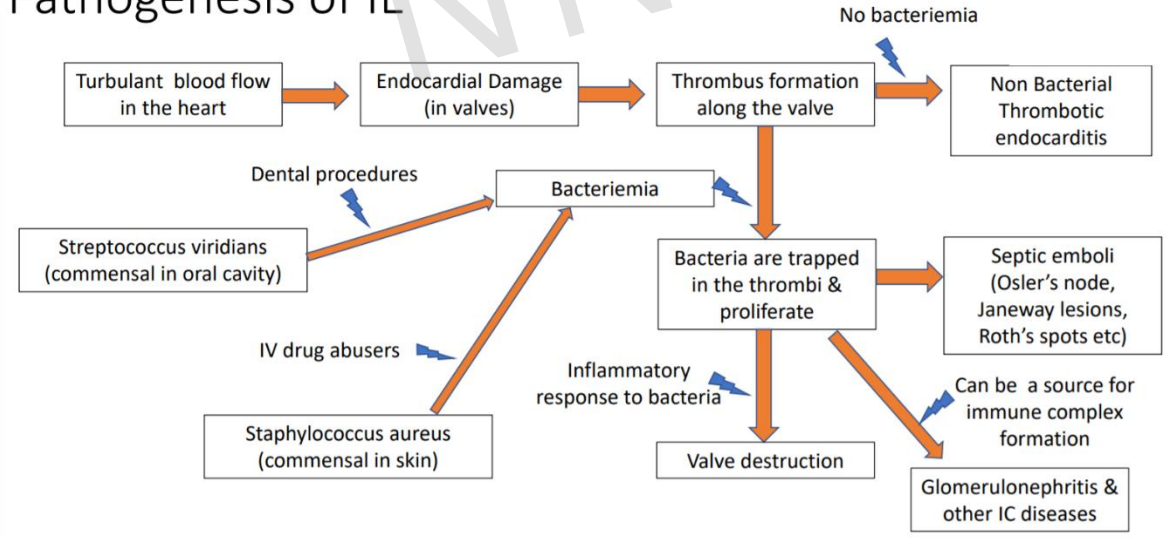
Pathogenesis of IE


Turbulant blood flow in the heart
Endocardial Damage (in valves)
Thrombus formation along the valve
No bacteriemia
Non Bacterial Thrombotic endocarditis
Dental procedures
Bacteriemia
Streptococcus viridians (commensal in oral cavity)
Bacteria are trapped in the thrombi & proliferate
Septic emboli (Osler's node, Janeway lesions, Roth's spots etc)
IV drug abusers
Inflammatory response to bacteria
Can be a source for immune complex formation
Staphylococcus aureus (commensal in skin)
Valve destruction
Glomerulonephritis & other IC diseases

ACUTE IE	SUBACUTE IE (More Common)
High Virulence organism	Low Virulence organism
Staph aureus (M/c) [SKIN]	Streptococcus Viridians (M/c) [Dental] **OVERALL MOST COMMON TYPE**
Fever, Chills present	Fever, Chills absent
Other manifestations present	Other manifestations are present
	Valve Damage less severe as compared to acute

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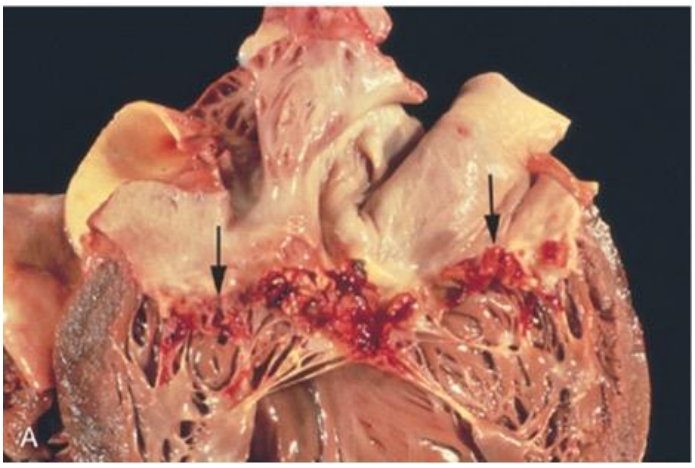
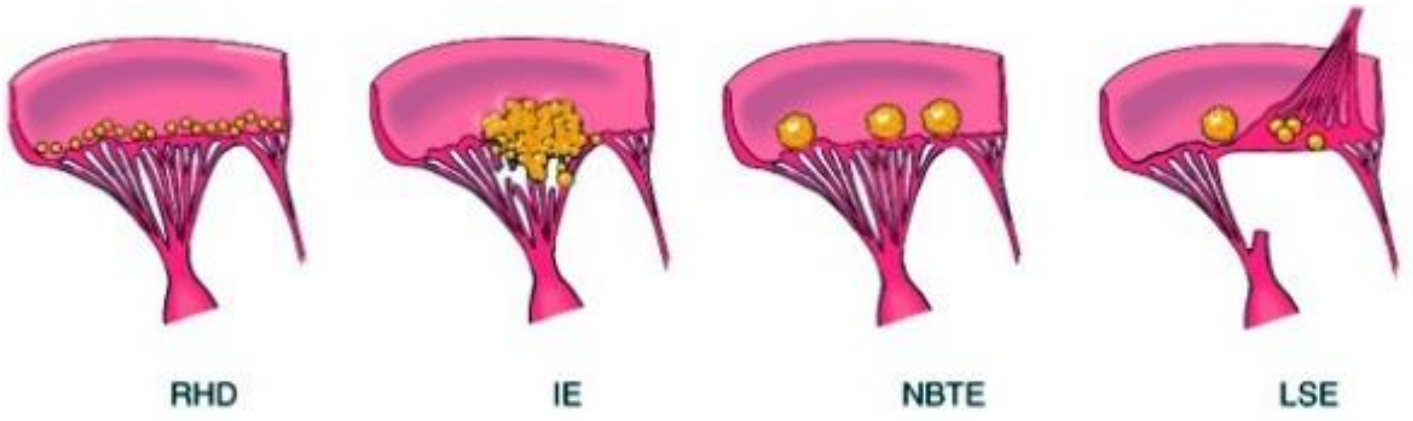
Gross Pathology

Vegetations: Large, Friable, **Hemorrhagic**, along valves, usually destroying valves, trickling down the chordae tendineae.

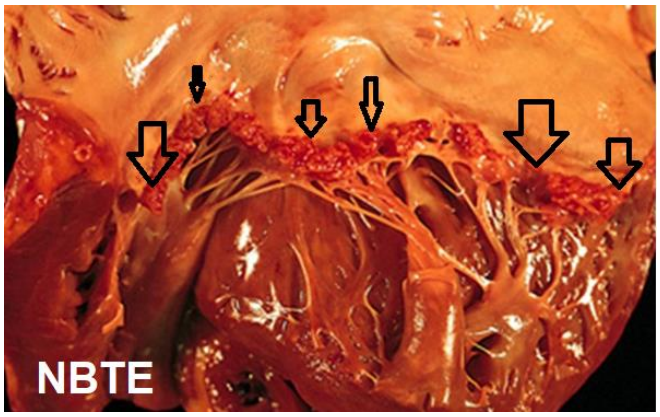
Why?

- ➔ Friable; due to bacterial infection and superadded inflammatory process.
- ➔ Large; due to stacking up of bacteria
- ➔ Hemorrhagic; because of thrombus formation





Diagrammatic comparison of the lesions in the four major forms of vegetative endocarditis. The rheumatic fever phase of RHD (rheumatic heart disease) is marked by a row of warty, small vegetations along the lines of closure of the valve leaflets. IE (infective endocarditis) is characterized by large, irregular masses on the valve cusps that can extend onto the cords. NBTE (nonbacterial thrombotic endocarditis) typically exhibits small, bland vegetations, usually attached at the line of closure. One or many may be present. LSE (Libman-Sacks endocarditis) has small or medium-sized vegetations on either or both sides of the valve leaflets.



NBTE Vegetations

- Hemorrhagic
- Small
- Bland
- Does not involve the chordae tendineae

Treatment

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EMPIRIC REGIMENS for endocarditis while culture results are pending should include agents active against staphylococci, streptococci, and enterococci.

Vancomycin 1 g every 12 hours intravenously **plus ceftriaxone** 2 g every 24 hours

For penicillin-susceptible viridans streptococcal endocarditis

penicillin G, 18 million units intravenously either continuously or in four to six equally divided doses, or ceftriaxone, 2 g intravenously once daily for 4 weeks, is recommended

The duration of therapy can be shortened to 2 weeks if gentamicin, 3 mg/kg intravenously every 24 hours, is used with penicillin or ceftriaxone.

For the patient unable to tolerate penicillin or ceftriaxone, vancomycin, 15 mg/kg intravenously every 12 hours for 4 weeks

Endocarditis caused by *S pneumoniae, S pyogenes* (group A streptococcus), or groups B, C, and G streptococci is unusual. *S pneumoniae* sensitive to penicillin

penicillin 18 million units intravenously either continuously or in four to six equally divided doses or cefazolin 6 g intravenously either continuously or in three equally divided doses, or ceftriaxone 2 g daily intravenously for 4 weeks

The addition of vancomycin and rifampin to ceftriaxone may be considered in patients with *S pneumoniae* strains

For enterococcal endocarditis

ampicillin,2 g intravenously every 4 hours, or penicillin G, 18–30 million units intravenously continuously or in six equally divided doses plus gentamicin, 1 mg/kg intravenously every 8 hours

duration of therapy is 4–6 weeks

For enterococcal resistant strains –endocarditis

-vancomycin plus gentamicin

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For methicillin-susceptible *S aureus* isolates

nafcillin or oxacillin, 12 g intravenously daily given continuously or in four to six divided doses or cefazolin, 6 g intravenously daily given continuously or in three divided doses for 6 weeks,

methicillin-resistant *S aureus*

vancomycin, 30 mg/kg/day intravenously divided in two or three doses, or daptomycin intravenously at greater than or equal to 8 mg/kg/day.

coagulase-negative staphylococci—a common cause of prosthetic valve endocarditis

A combination of vancomycin, 30 mg/kg/day intravenously divided in two or three doses for 6 weeks; rifampin, 300 mg every 8 hours for 6 weeks; and gentamicin, 3 mg/kg intravenously every 8 hours for the first 2 weeks, is recommended for prosthetic valve infection

HACEK organisms are slow-growing, fastidious gramnegative coccobacilli

ceftriaxone (or another third-generation cephalosporin), 2 g intravenously once daily for 4 weeks

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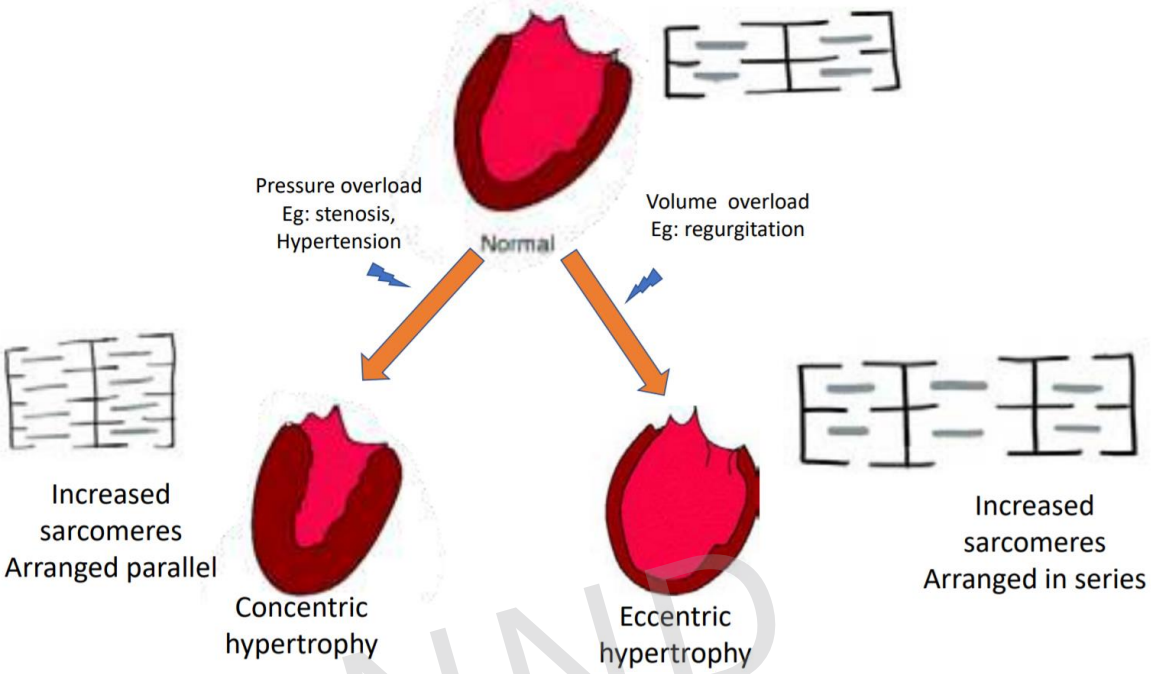
Acute Heart Failure

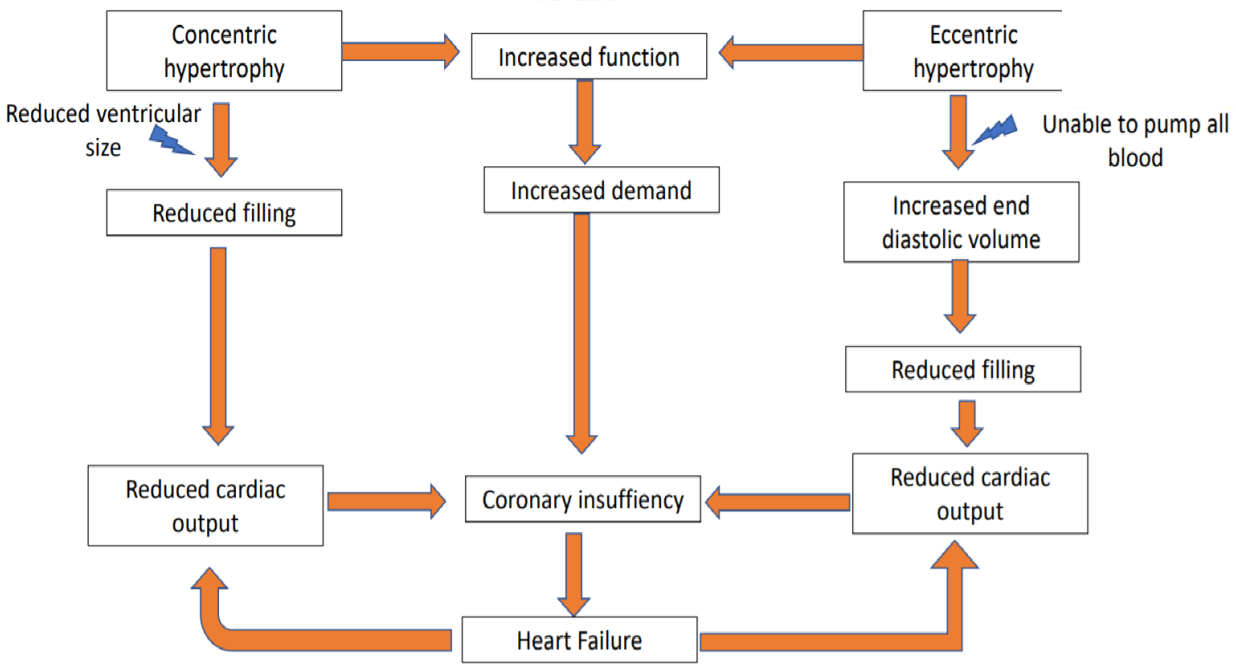
Case: A 50-year-old hypertensive patient with poor drug compliance presented with progressively increasing dyspnoea for 3 days. He complaint of episodes of breathlessness 3-4 hours during midnight (PND) and has to wake up from sleep. On examination BP is 180/110 mmHg, pulse 120/min, oxygen saturation 85%, LV S3 present (LVF) and lungs have bilateral crepts (Pulmonary Edema). What is the clinical diagnosis?

Pathophysiology



Q. Best indicator of hypertrophy of myocardium on gross examination

A. Weight of the Heart (NOT the thickness of the myocardium)



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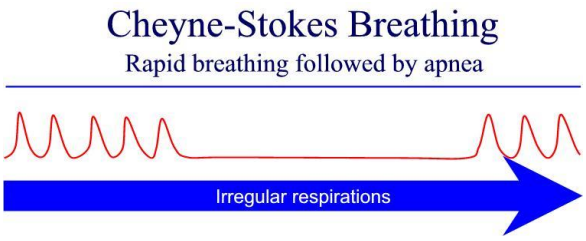
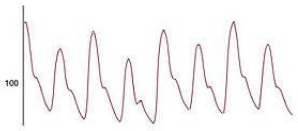
Clinical Features

1. Dyspnea (M/C)- d/t Pulmonary congestion and Pulm Edema
2. PND (Most Specific)
3. Orthopnea
4. Cheyne Strokes Breathing



Examination Findings:

1. Pulsus Alternans



2. Diffuse Apex because heart does not contract effectively.
   Area of Apex > 2.5 sq. cm

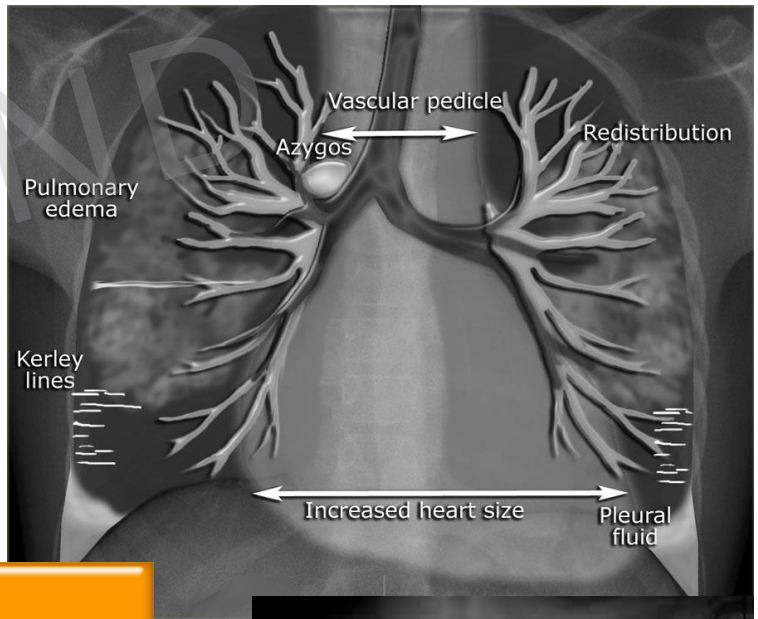
3. Kussmaul Sign- s/o RVF

4. S3- Systolic Failure (Contractile dysfunction)
   S4- Diastolic Failure (Stiff ventricles)

XRAY Findings

All findings d/t ↑sed PCWP leading to pulmonary Edema

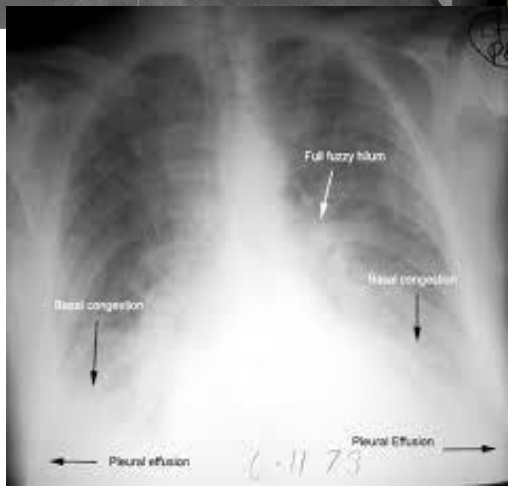
- Increased Heart Size
- Kerly Lines
- Pulmonary Edema
- Increased size of vascular pedicle



NON Cardiogenic Edema (eg- ARDS)

- No batwing appearance
- No Kerly B lines
- Diffuse opacifications

Stage of Congestive Heart Failure		
Stage 1 Redistribution PCWP 13-18 mmHg	→	Redistribution pulmonary vessels Cardiomegaly Broad vascular pedicle (non acute CHF)
Stage 2 Interstitial edema PCWP 18-25 mmHg	→	Kerley lines Peribronchial cuffing Hazy contour of vessels Thickened interlobar fissure
Stage 3 Alveolar edema PCWP > 25 mmHg	→	Consolidation Air bronchogram Cottonwool appearance Pleural effusion



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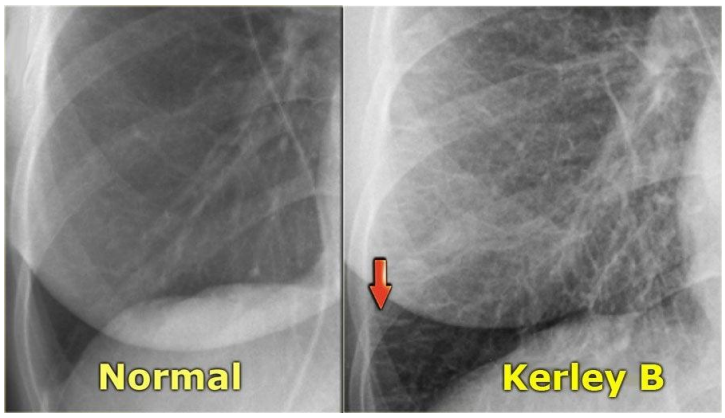


Criteria for Cardiomegaly in Cardio-Thoracic ratio

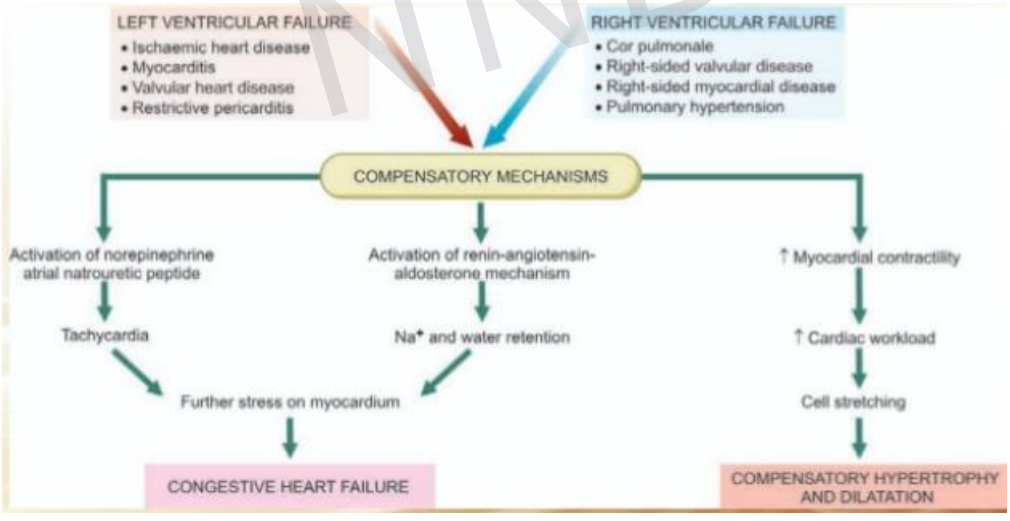
- ✓ Adults: > 0.5
- ✓ Infants: > 0.6

Management

Acute Cardiac Failure (Sudden decrease in Cardiac Output)

- ➢ Diuretics: I/V Furosemide
- ➢ Dilators
- ➢ Inotropic Agents: Digoxin, **Dopamine**, Dobutamine, Norepinephrine

Chronic Cardiac Failure (Gradual reduction of CO)



- ○ Beta Blockers
- ○ ACE Inhibitor
- ○ ARBs
- ○ Mineralocorticoid Receptor Antagonist (MRA)- Spironolactone

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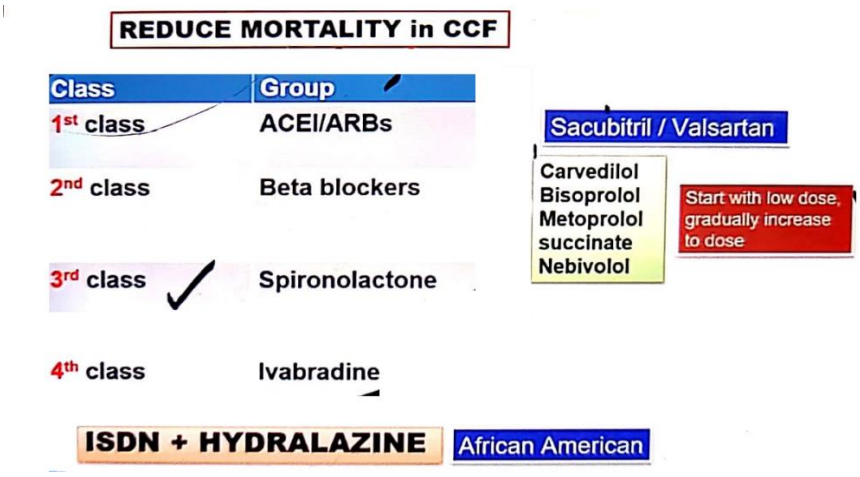

- Calcium sensitizer: PIMOBENDAN, LEVOSIMENDAN
- Direct myosin activator: OMECAMITIV
- Recombinant BNP: NESIRITIDE (I/V) (S/E- Hypotension)
  Goes under metabolism by Neprilysin (Neutral endopeptidase)
- Neprilysin Inhibitor: ECADOTRIL and SACUBITRIL
- Neprilysin Inhibitor + ACE Inhibitor: OMAPATRILAT + SAMPATRILAT

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Dilated Cardiomyopathy

Case: A 60-year-old female presented with 1-year history of dyspnea. There is no other significant past history. On examination pulsus alternans+, BP-110/80, JVP is raised, apex beat is diffuse, LVS3 present, pedal edema, no murmur present. Echocardiogram shows diffuse hypokinesia with EF 25%. What is the most likely diagnosis?

Clues: 1. Pulsus Alternans
2. Diffuse apex beat
3. EF 25%

Clinical approach towards diagnosis

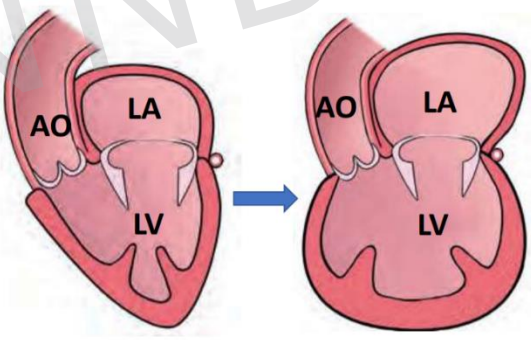
1. Pulses Alternans + Diffuse Apex → Dilated Cardiomyopathy
2. Normal Pulse + Localised Apex → Restrictive Cardiomyopathy
3. Bifid Pulse (Bisferience variant- shortened second peak) + Double Apex → HOCM

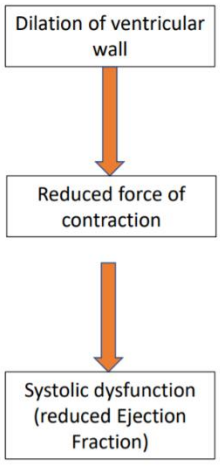
Causes & Pathogenesis

Causes DCM

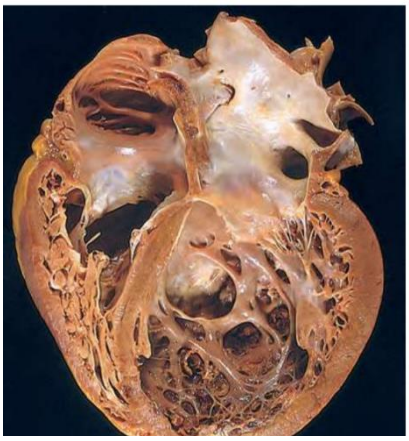
- Genetic (MC cause)
  - Titin mutataion- AD
  - DMD, BMD
- Myocarditis
- Alcohol
- Toxins (cobalt)
- Post partum
- Iron overload
- Takotsubu cardiomyopathy (catecholamines induced)

Dilated Cardiomyopathy

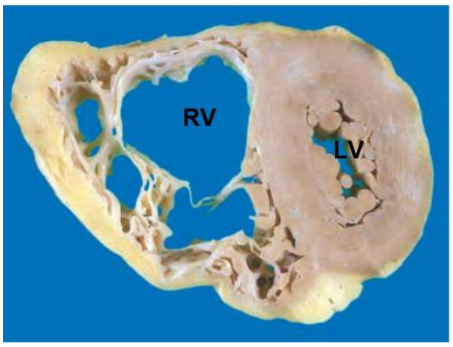


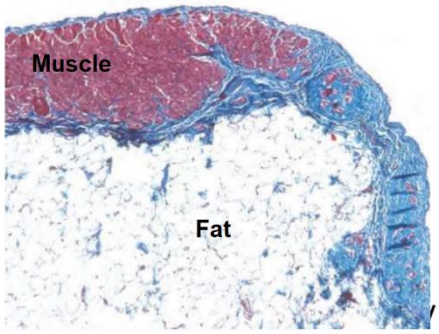


Gross DCM



Arrhythmogenic right ventricular DCM **(AR-DCM)**





Right ventricular muscle replaced by fat

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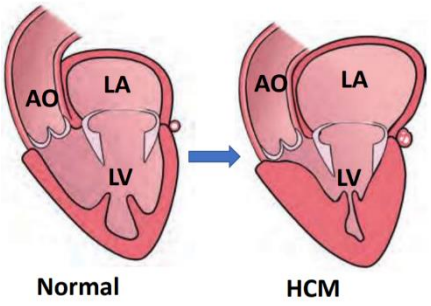
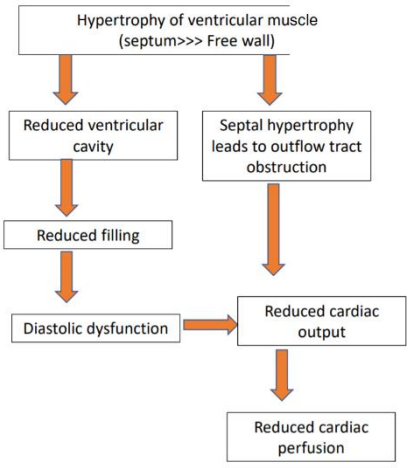
Hypertrophic Cardiomyopathy





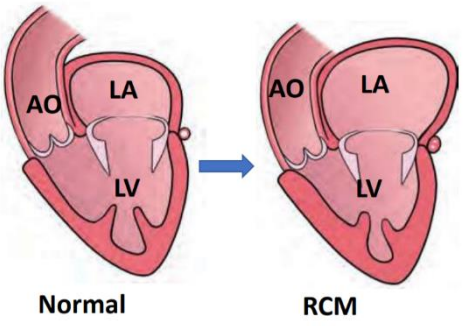
Gross HCM

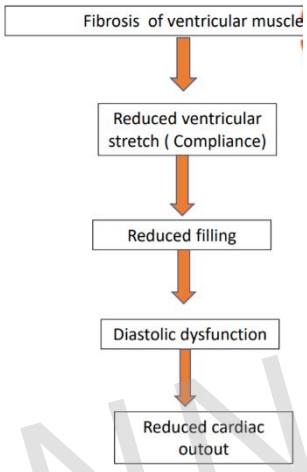
Causes HCM

- Genetic (MC cause)
- Myosine heavy chain (MYH 7) (most common)
- Myosine binding protein C (MYBP-C)
- Troponin I, troponin T, alpho tropomyosin

** All murmurs increase with increase in blood volume, except that of HOCM which decreases with increase in blood volume*

Restrictive Cardiomyopathy





Causes of RCM

- Endomyocardial fibrosis
- Loeffler endomyocarditis
- Endocardial fibroelastosis
- Prior surgery
- Radiation
- Amyloidosis

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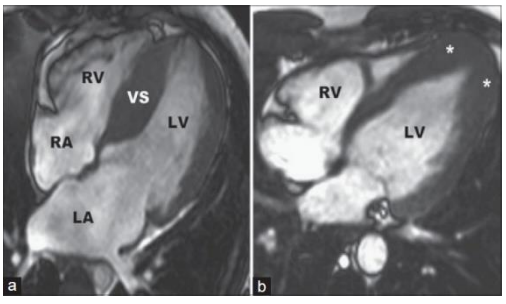
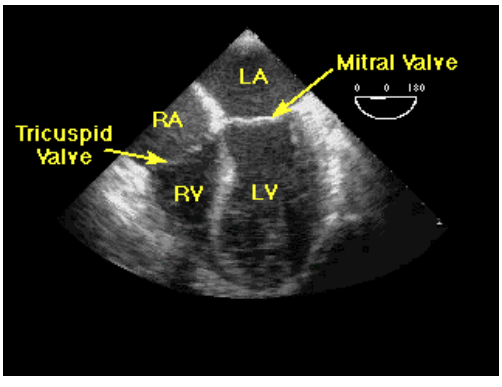
Radiology

1. Cardiac MRI-

- Myocardial Scar: Late gadolinium enhancement
- Amyloidosis – Antemortem diagnosis on cardiac MRI
- Hemochromatosis- Antemortem diagnosis on cardiac MRI



2. Echocardiography



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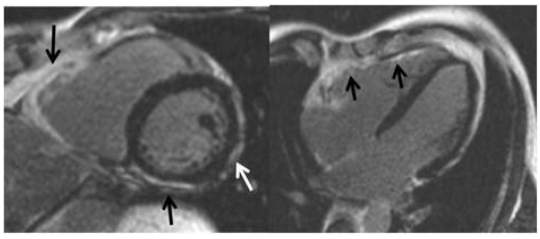
Arrythmogenic RV Cardiomyopathy (ARVC)

Fibrofatty replacement of the RV Tissue (Black Arrows)

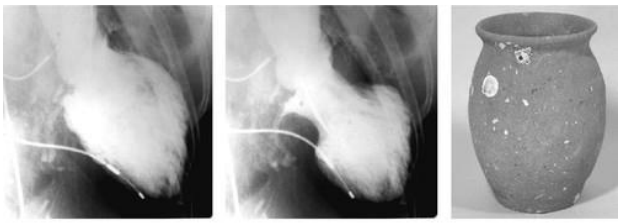


Takotsubo Cardiomyopathy

Apex- Akinesis, Basal- Hypercontractile

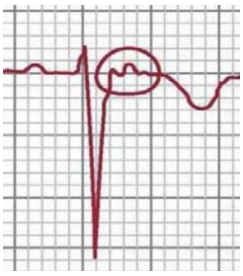
A- Diastolic

B- Systolic



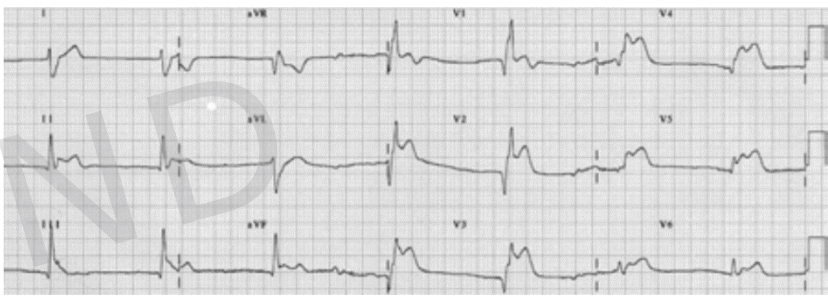
ECG Findings

1. Lead V1- Slurring of ECG wave after the QRS Complex (Epsilon Wave) → Seen in **ARVC**



2. **Takotsubo cardiomyopathy**

- Shows ST Elevation
- Mimics Myocardial Infarction
- (Chest Pain, Elevated Troponin)
- Echo- Dilatation of ventricle apex



3. Yamaguchi Cardiomyopathy (HOCM Variant)

- In V4, V5, V6
- Tall QRS (R wave >25 cm)
- Giant T wave inversion
- T wave depth > 10cm
- Apical Hypertrophy is seen

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Treatment

Treatment depends on the cause

- Steroids- sarcoidosis
- Alpha+ betablocker-Tako Tsubo CMP
- Bromocriptine-Peripartum CMP
- Betablocker-HOCM
- Phlebotomy-Hemochromatosis
- Liver transplant-Familial amyloidosis

*Peripartum CMP- Prolactin fragments which are cardiotoxic, are increased in the last trimester of pregnancy till 5-6 months postpartum.

*Beta-blockers decrease the myocardial contractility resulting in relief in obstruction in HOCM

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CONSTRICTIVE PERICARDITIS

Case: A 30-year-old patient c/o swelling over leg progressing to abdomen for 3months. On examination pulsus paradoxus, JVP raised with deep y descent, apex beat non localised, third heart sound best heard with diaphragm of stethoscope. There is no murmur heard. What is the diagnosis?

Causes of Pulsus Paradoxus

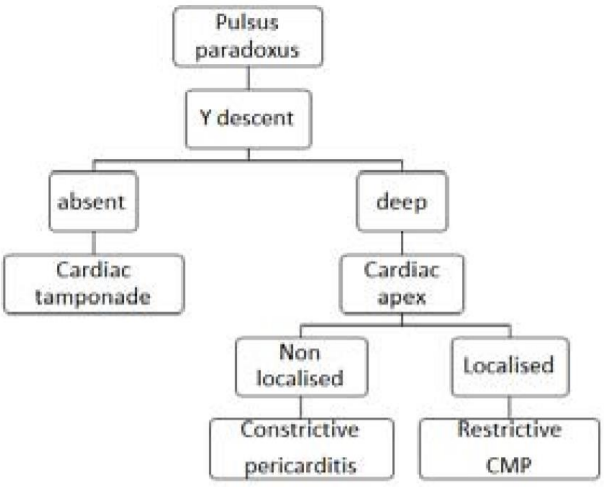
Respiratory	Cardiac	Others
• Severe brochial asthma • Tension pneumothorax • COPD	• Cardiac temponade • Constrictive pericarditis • Pericardial effusion • Restrictive cardiomyopathy	• Anaphylactic shock • Obesity

- Acute- Cardiac Temponade
  Chronic- RCMP and Constrictive pericarditis

- Deep y descent in JVP: Caused by RCMP & Constrictive pericarditis

- Localised Apex Beat- RCMP
  Diffuse Apex Beat – Pericardial disease

- Third Heart Sound
  - S3 – Low-pitched
  - Pericardial Knock- High pitched (Heard with diaphragm of stethoscope), seen only in CONSTRICTIVE PERICARDITIS
- RCMP- MR murmur, Pericardial diseases have NO murmur



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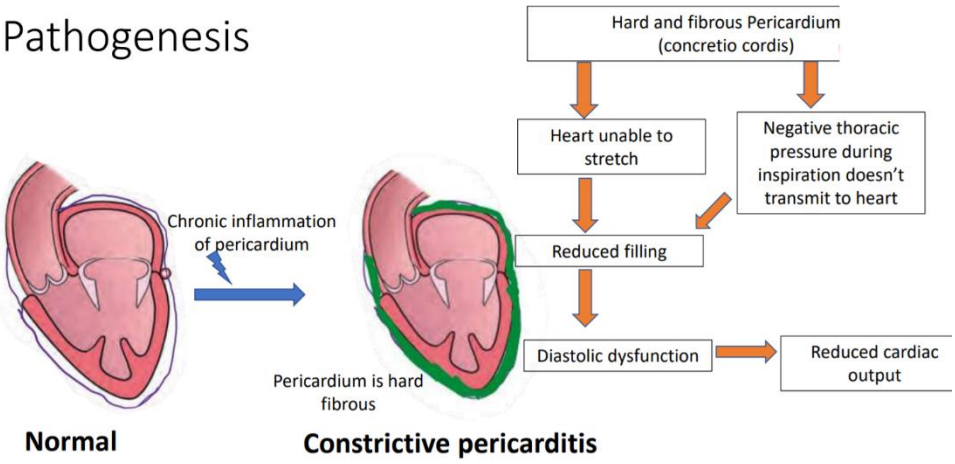
Pathogenesis

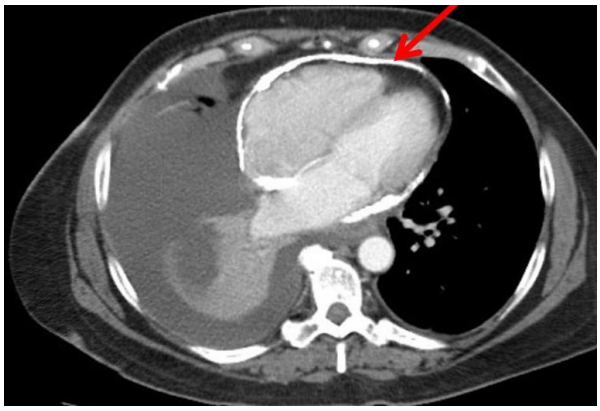


Causes

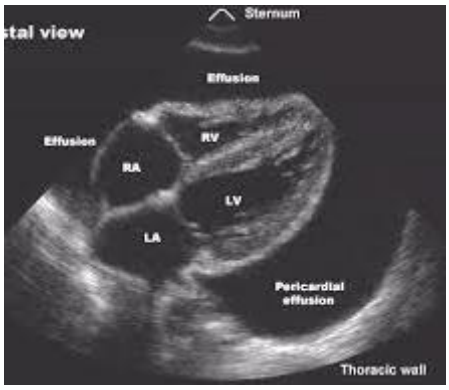
- Idiopathic (MC in developed countries)
- Infections (MC in developing countries)
  - Tuberculosis
  - Viral pericarditis (Coxsackie virus, echovirus)
- Previous surgery
- Trauma
- Radiation
- Inflammation (Rheumatoid, SLE)
- Neoplastic (lung, breast carcinoma)
- Uremia

Radiology

Cardiac CT: Calcification of the pericardium

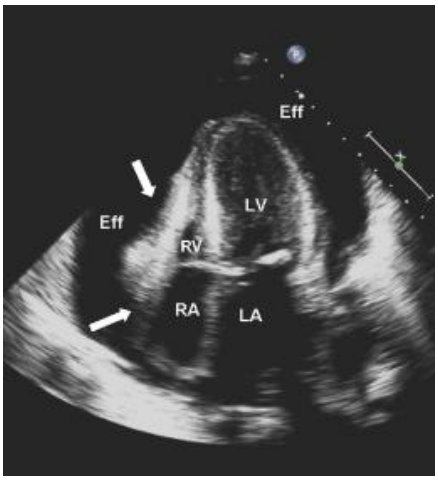


Echocardiography:



Echo Findings in cardiac tamponade

- Presence of moderate and large pericardial effusion.
- Swinging of the heart within the effusion
- Reversal of right atrial and right ventricular diastolic transmural pressures.
- Cardiac chamber collapse is a common finding in cardiac tamponade.
- The right atrium and right ventricle are the most likely to collapse when intrapericardial pressure exceeds intracardiac pressure within any particular chamber.



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ECG FINDINGS -Acute Pericarditis

1. Diffuse ST Elevation in ALL leads.

2. PR Segment Depression in Lead II

3. No Pathological Q waves or reciprocal changes (seen in MI)

4. Oscillation of the heart in pericardial fluid showing in ECG as alternate Low and High voltage QRS Complex (Electrical Alternans)

Treatment of Pericardial diseases

1. Acute pericarditis- NSAIDS; if refractory – Colchicine or steroids

2. Constrictive pericarditis – Pericardiectomy

3. Cardiac Tamponade- Pericardiocentesis under Echo guidance
1st line management although is the treatment of SHOCK.

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HYPERTENSION

Case: Patient presented with BP 150/90 mmHg measured on 3 occasions. There is no significant past medical history. What will be next step in management of this patient?

Physiology

Pulse Pressure = SBP- DBP,

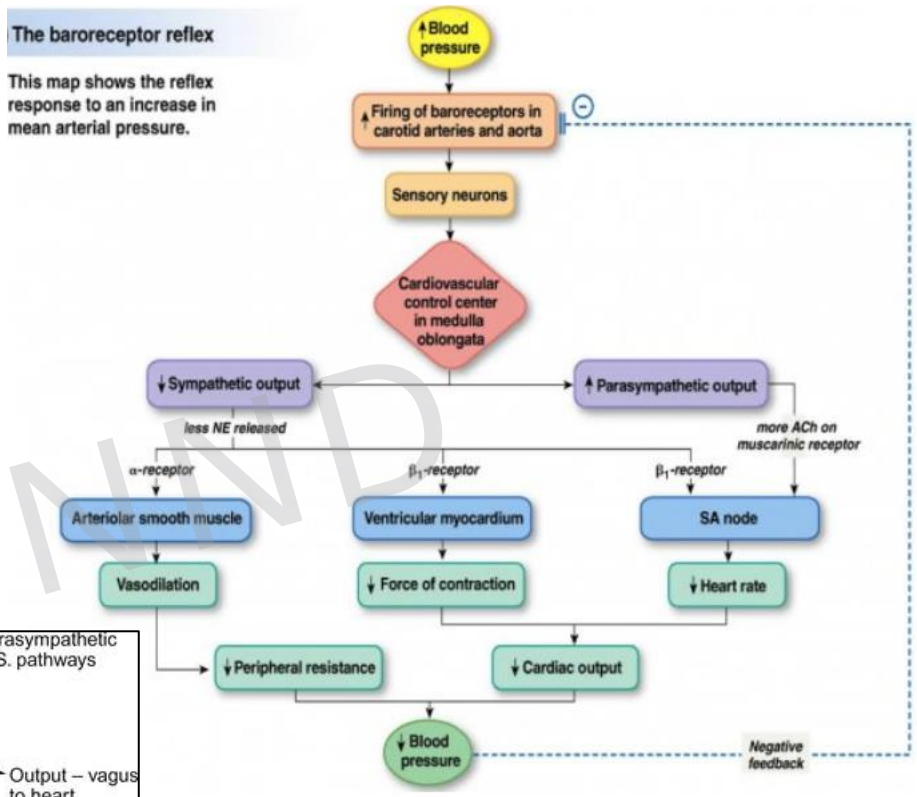
: Directly proportional to Stroke Volume

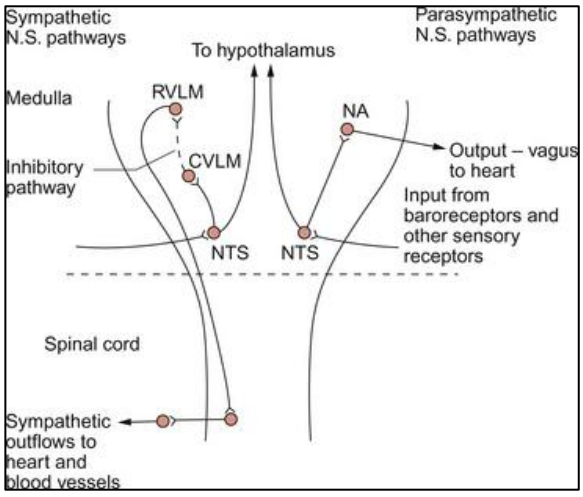
: Inversely proportional to arterial Compliance

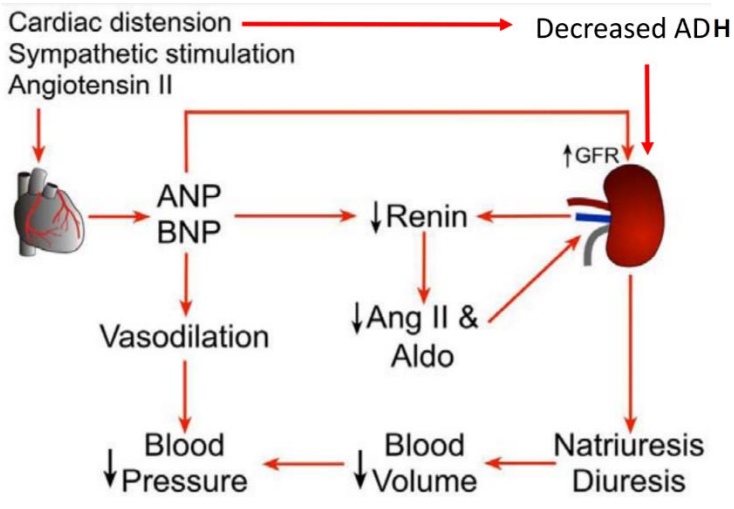
Mean Arterial Pressure = DBP + (SBP/3)

Baroreceptors are:

- Stretch Receptors
- a/k/a Buffer nerves
- **Carotid sinus BaroR** are just at the bifurcation of the CCA in the ICA (IX CN).
  More sensitive
- **Aortic Arch BaroR** are located along the arch of aorta (X CN)







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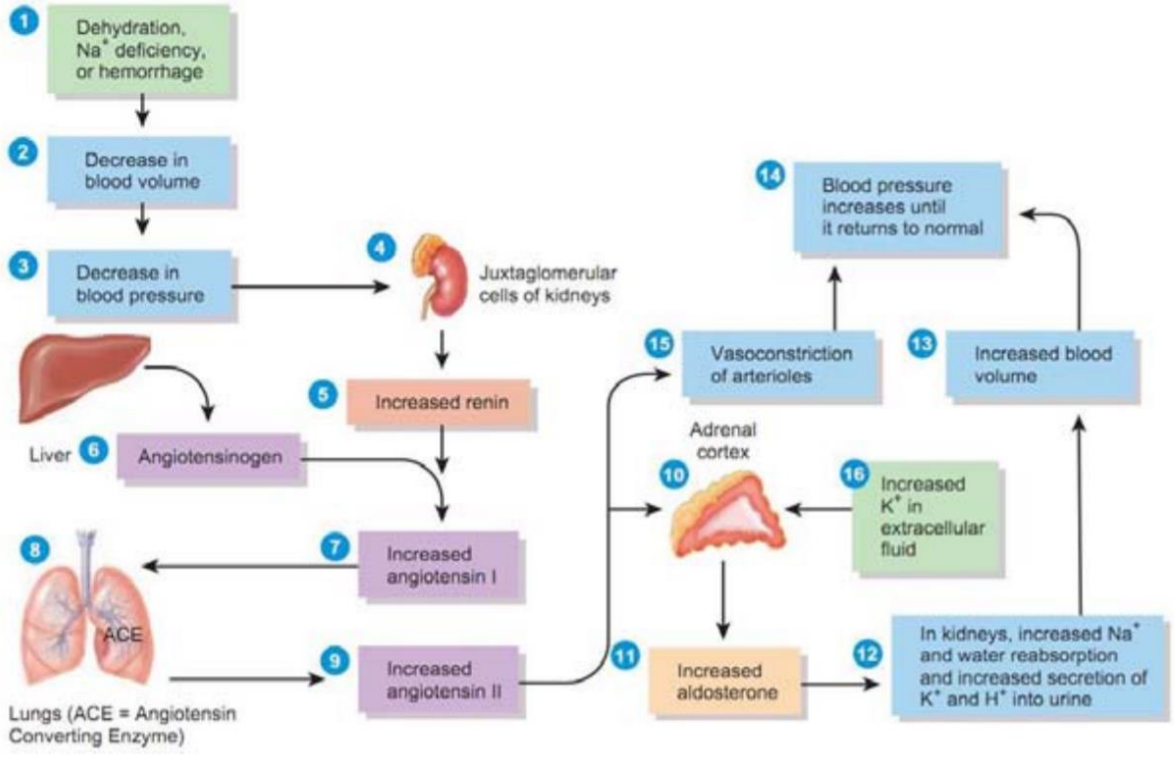
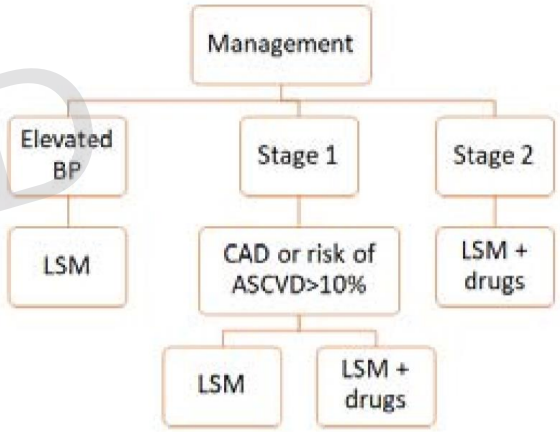

1 Dehydration, Na+ deficiency, or hemorrhage
2 Decrease in blood volume
3 Decrease in blood pressure
4 Juxtaglomerular cells of kidneys
5 Increased renin
Liver
6 Angiotensinogen
7 Increased angiotensin I
8 ACE
Lungs (ACE = Angiotensin Converting Enzyme)
9 Increased angiotensin II
10 Adrenal cortex
11 Increased aldosterone
12 In kidneys, increased Na+ and water reabsorption and increased secretion of K+ and H+ into urine
13 Increased blood volume
14 Blood pressure increases until it returns to normal
15 Vasoconstriction of arterioles
16 Increased K+ in extracellular fluid

Classification – AHA Guidelines

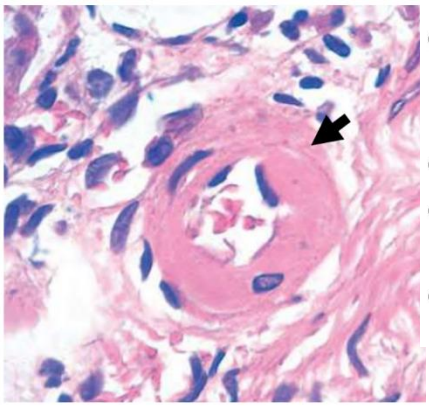
CATEGORY	SYSTOLIC BP (MM HG)		DIASTOLIC BP (MM HG)
NORMAL	<120	AND	<80
ELEVATED BP	120-129	AND	<80
STAGE 1	130-139	OR	80-89
STAGE 2	≥ 140	OR	≥ 90
HYPERTENSIVE CRISIS	≥ 180	OR	≥ 120



Pathogenesis

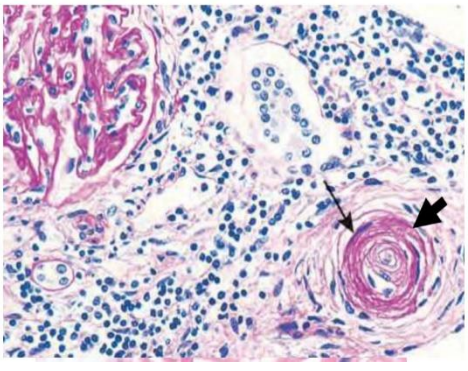
Hypertension Changes: Hyaline arteriosclerosis

- Hyaline material due to leakage of plasma (due to endothelial injury)
- Also increased matrix synthesis by the vessel wall as response to stress
- Best seen in **RENAL ARTERIOLES**
- Can also be seen in old age and diabetes



Hypertension Changes: Hyperplastic arteriosclerosis

- Smooth muscle proliferation (**Onion Skin appearance**)
- Fibrinoid necrosis
- Seen in malignant hypertension
- Renal arterioles



Treatment

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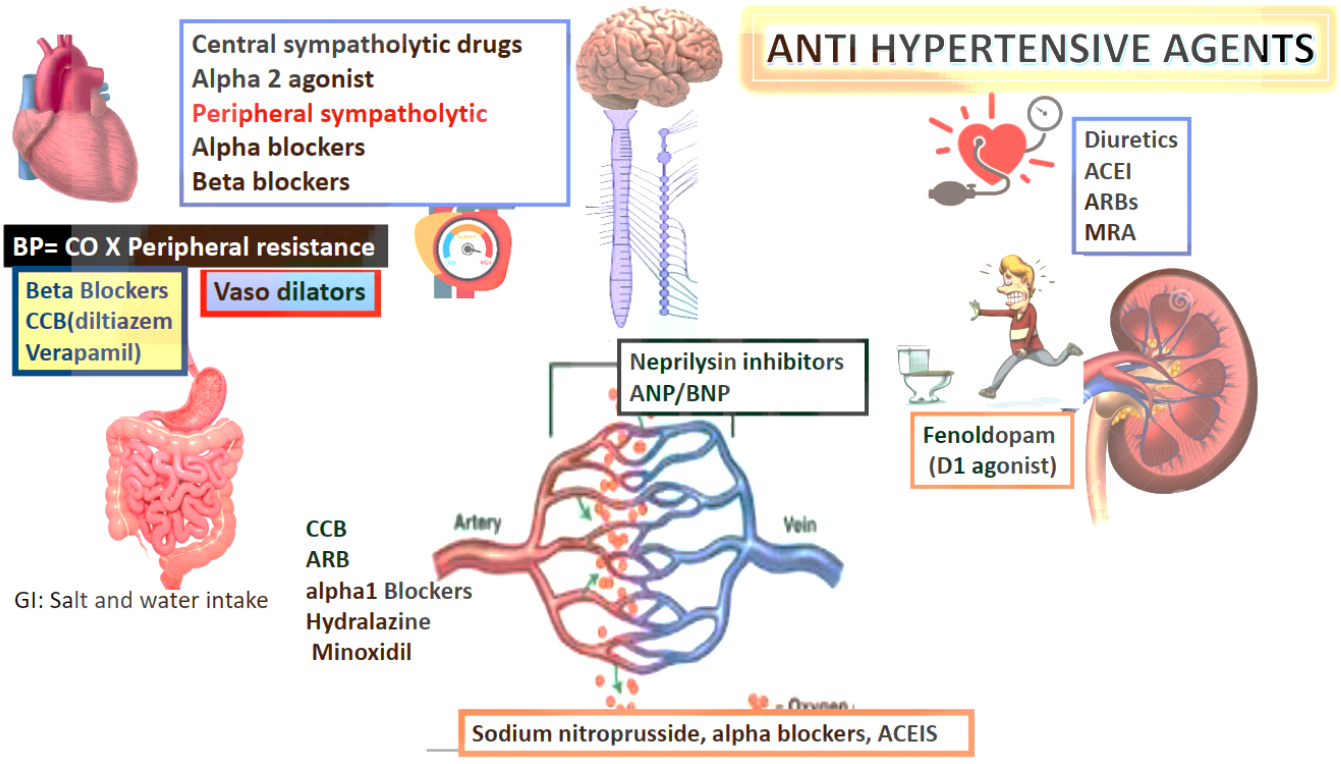

- Fenoldopam- D1 Agonist (intravenous)

➔ HTN + T2DM : ACEI/ ARB/ CCB (NO Diuretics / Beta blockers, masks hypoglycaemia)

➔ HTN + Hyperlipidemia: ACEI/ ARBs/ CCB/ Alpha Blockers (prazosin)
(NO Diuretics / Beta blockers, as cause lipid dysregulation)

➔ HTN + CAD= Beta Blockers/ CCB – Diltiazem/ ACEI/ARBs (No Arteriolar Vasodilators as they cause sudden hypotension leading to reflux tachycardia worsening of Angina)

➔ HTN + Asthma/ COPD= CCBs/ Diuretics/ ACEI (No non-selective beta blockers as they cause bronchoconstriction)

➔ HTN due to Pheochromocytoma = NON SELECTIVE IRREVERSIBLE ALPHA BLOCKER
Eg. PHENOXY BENZAMINE
(No Beta blockers, as they cause uncontrolled alpha action causing severe vasoconstriction leading to severe hypertension)

➔ HTN due to Pregnancy= Methyldopa / Labetalol (Crisis-1st line drug DOC)/ Hydralazine

List of drugs useful in Hypertensive emergency crisis:

- ✓ Hydralazine
- ✓ Esmolol (short acting beta blocker)
- ✓ Labetalol (beta blocker with addl alpha blocking properties)
- ✓ Enelaprilat
- ✓ Nitroprusside (HTN with Aortic Dissection) (Contains cyanide- C/I in Pregnancy)
- ✓ Nicardipine, Clevidipine
- ✓ Fenoldopam (D1 Agonist acting on Renal vessels causing renal vessel dilatation)

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JNC Target Guidelines

GOAL	
<60yrs without CKD or DM-	<140/90
>60yrs without CKD or DM-	<150/90
Any age with CKD or DM or both	<140/90
First line drugs	Thiazides ACEI ARB CCB NO BETA BLOCKERS
Second line drugs	Beta blockers Alpha blockers

Pt >50yrs best respond to	Thiazides CCB
Pt <50yrs best respond to	ACEI Beta blockers
Pt with stroke- best to prevent stroke	ACEI +Thiazides

NND

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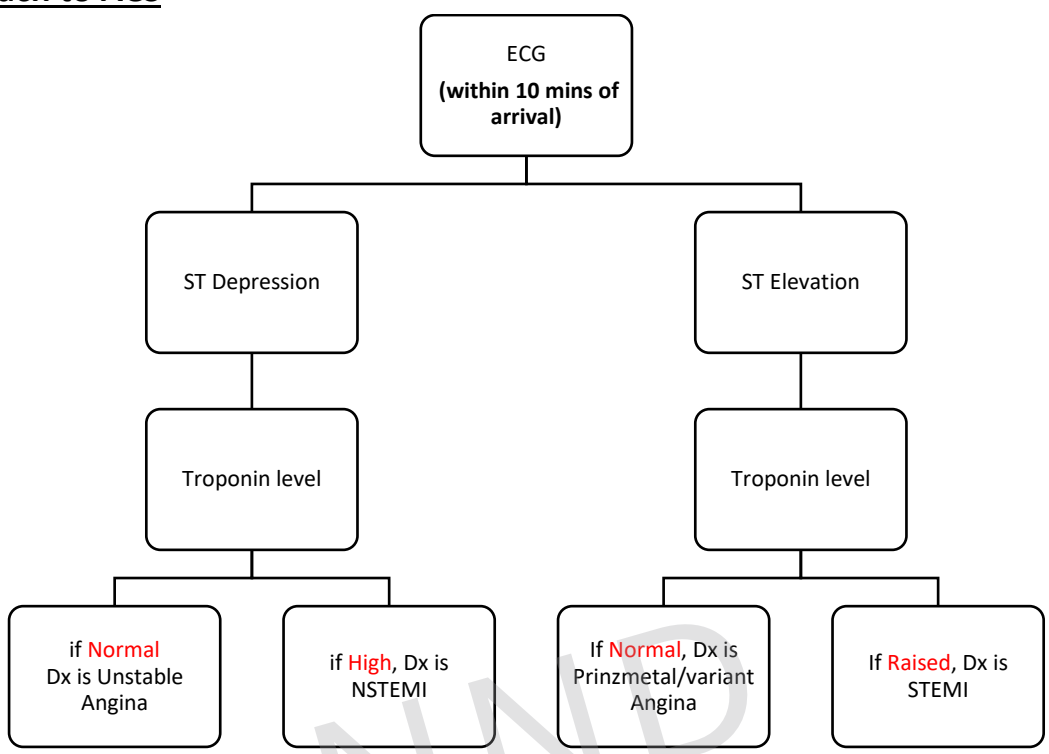
Acute Coronary Syndrome

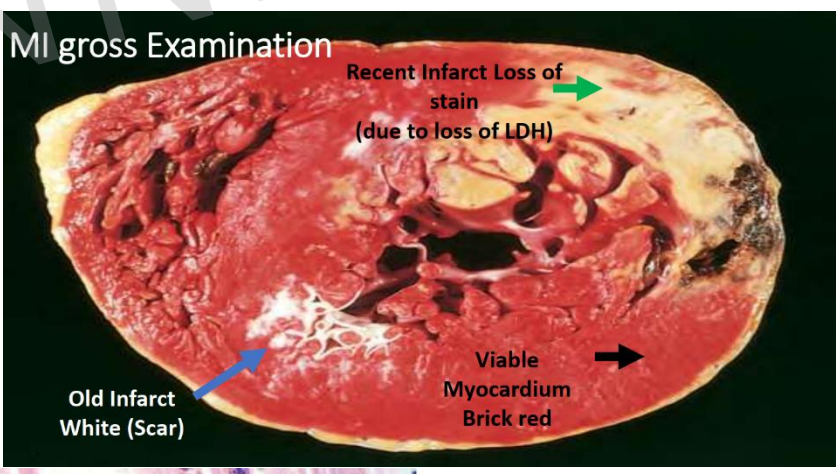
Case: A 45-year-old male presented with chest pain radiating to left arm. He also c/o of breathlessness and sweating. ECG shows ST elevation in anterior leads. Troponin levels are high. How will you classify this acute coronary syndrome?

Approach to ACS



Pathological features

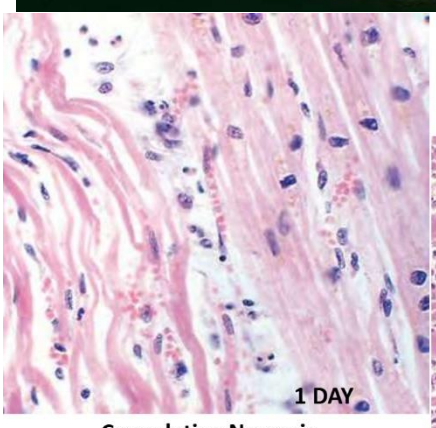
Gross examination stained by 'triphenyl tetrazolium chloride'



Microscopy: Start after 4 hours of an MI attack

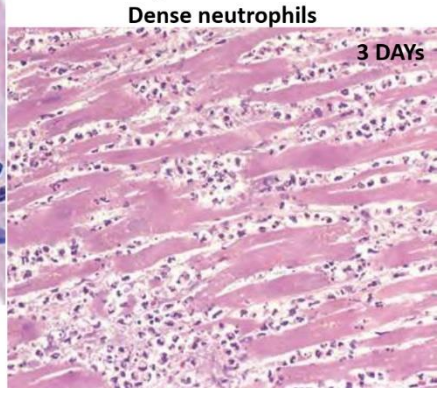
Dead cells → Inflammation →Fibrosis

- Image of Day 1 shows both:
  - Viable Myocardium (Nuclei Present)
  - Dead myocardium (lysis started)



Coagulative Necrosis
Occasional neutrophils

Coagulative Necrosis
Dense neutrophils



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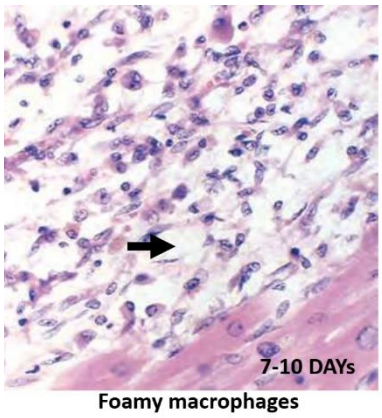
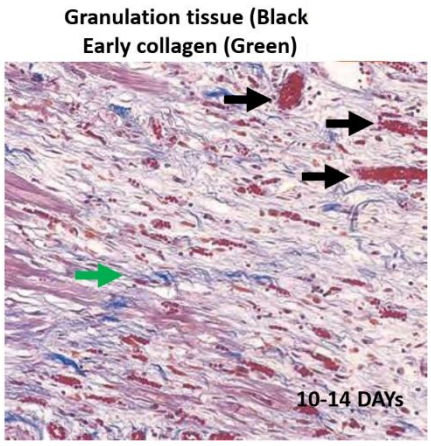
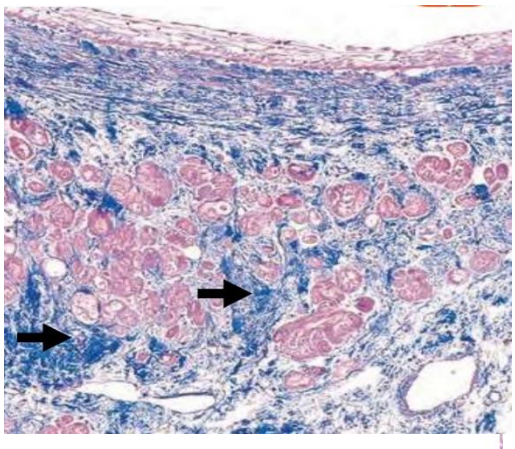
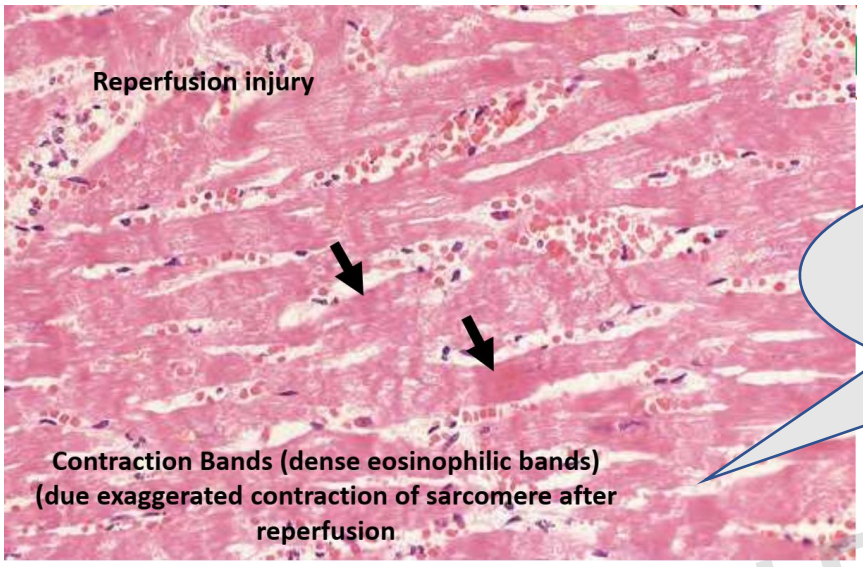






>2 Weeks

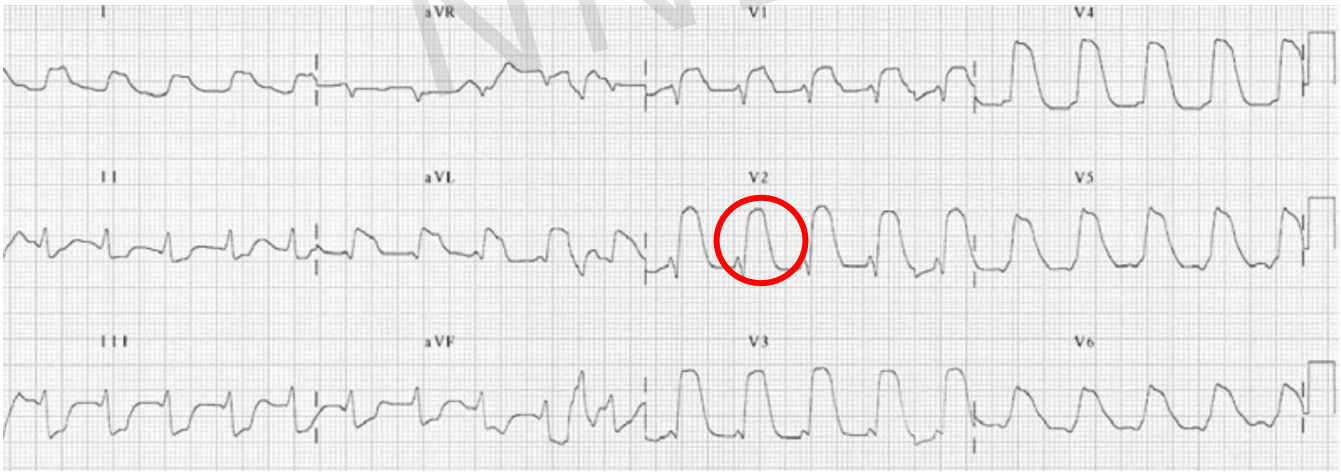
Dense Collagen (Masson trichrome Stain)


Reperfusion injury
Contraction Bands (dense eosinophilic bands)
(due exaggerated contraction of sarcomere after reperfusion

Coagulative necrosis +nt
No Neutrophilic infiltrates

Expected time- between 4-12 hrs

ECG Changes



- Lead 1 and aVL: ST Elevation
- Lead 2, 3, aVF: ST Depression (mirror image change)
- V1: ST Elevation
- V2: ST Elevation **(Grave stone sign)**
- V3, V4: ST elevation

Dx: Anterolateral STEMI with reciprocal changes in the inferior wall leads
(Probable site of thrombus: LCA)

T/t: Bypass Surgery

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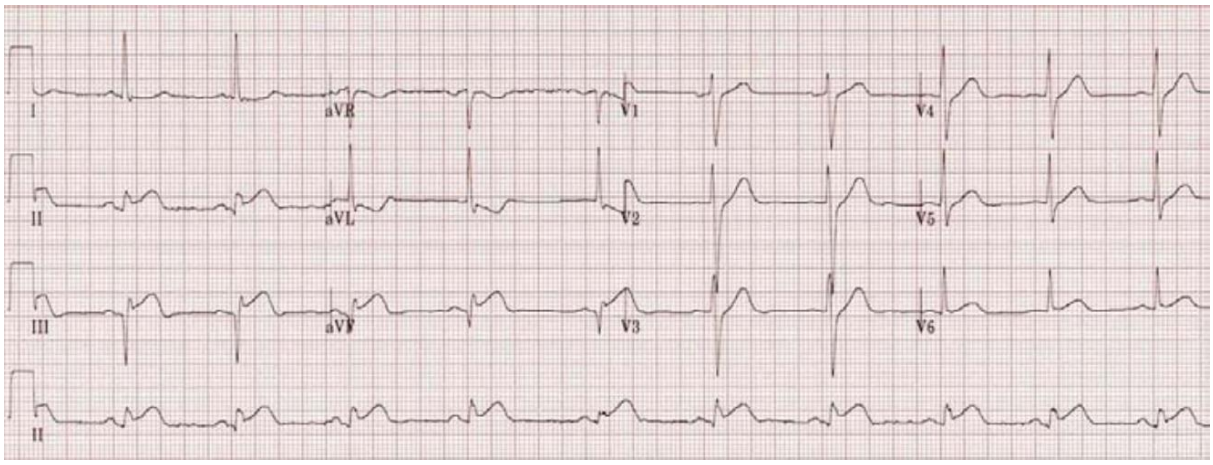
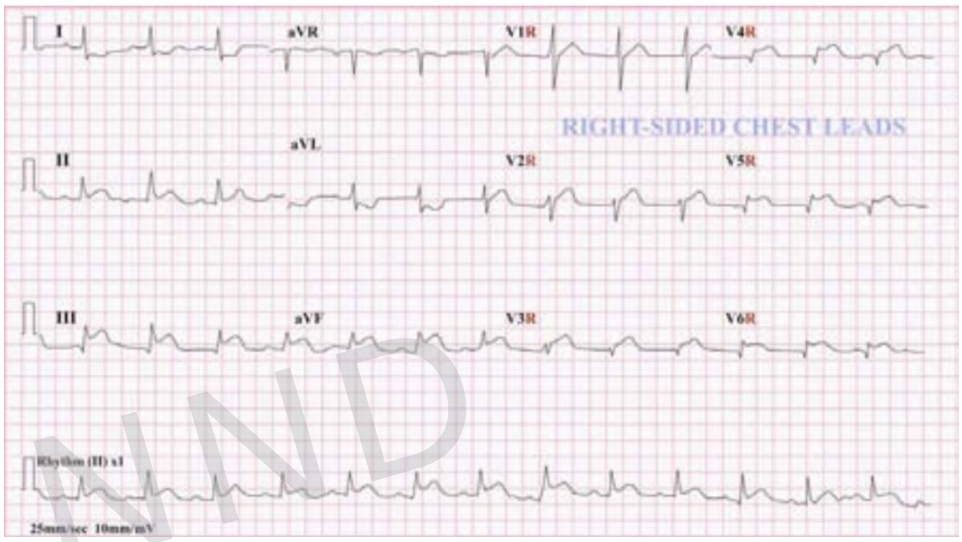
2. ECG #2



- Lead 1: Normal
- Lead 2&3: ST Elevation
- AVF: ST Elevation
- Dx: Inferior wall MI (RCA Thrombus)

3. ECG #3



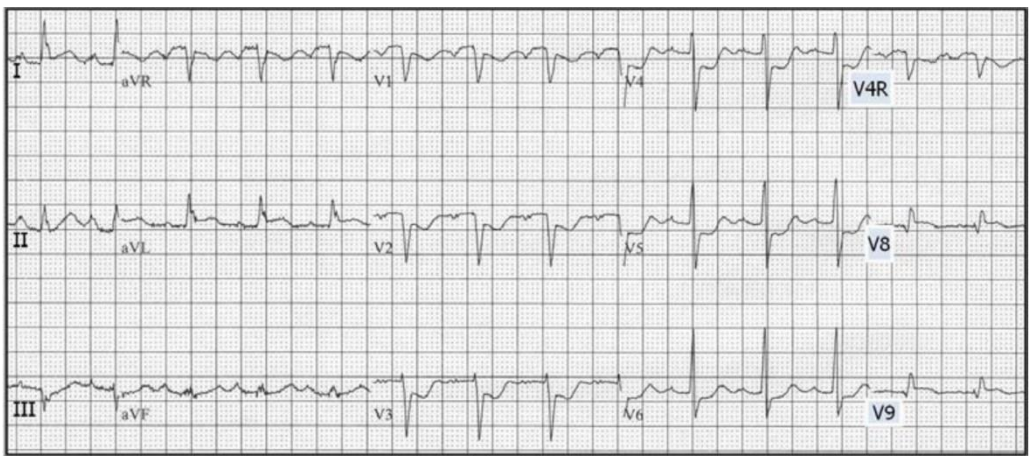
- Lead 1: ST Depression
- Lead 2, 3, AVF: ST Elevation
- Elevation in V3 to V6

Dx: Inf Wall MI + RV wall MI

T/t: IV Fluids

(Venodilators -c/i in RWMI)

4. ECG # 4



- No obvious changes
- ST Depression in V1, V2, V3
- V8, V9 k/a Extended Chest leads, put to detect Posterior wall MI
- V8, V9- ST Elevation
- Dx: Posterior wall MI

Treatment

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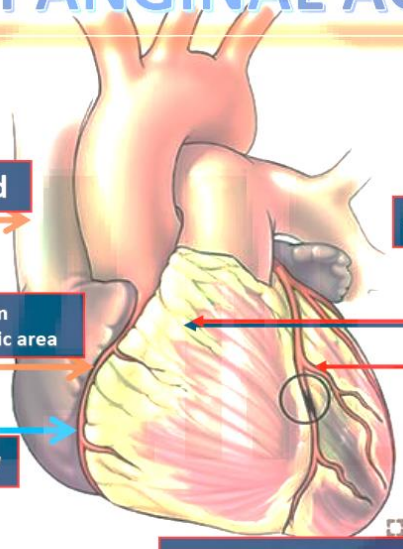
ANTI ANGINAL AGENTS



NITRATES

↓Work load

Re distribute Blood from non ischemic to ischemic area

NICORANDIL

↑Blood flow

IVABRADINE

↓(HR)Work load

Beta blockers

CCB

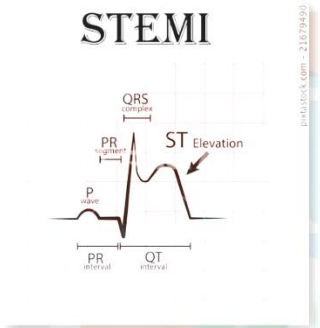
↓(HR)Work load
↑Blood flow

TRIMETAZIDINE
RANOLOSINE

ANTI OXIDANT
Na CHANNEL BLOCK

First line drugs
Beta blockers
CCB- Diltiazem
Nitrates

pFOX inhibitors
Trimetazidine
Ranolazine
I_f Na channel blocker
IVABADINE
K channel opener-
Nicorandil



S/L- NTG
MORPHINE- MI

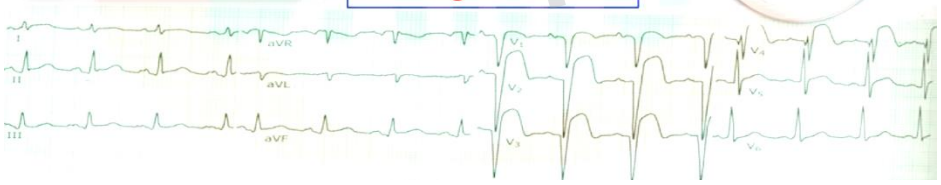
PETHIDINE
PENTAZOCINE

Anti platelets

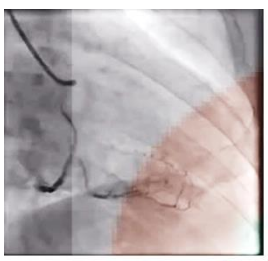
RE CANALISATION

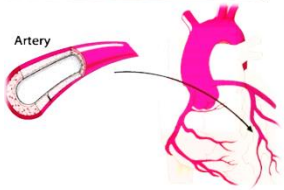
Primary angioplasty

Fibrinolytic therapy/
anticoagulants



Tachyarrhythmias





PTCA

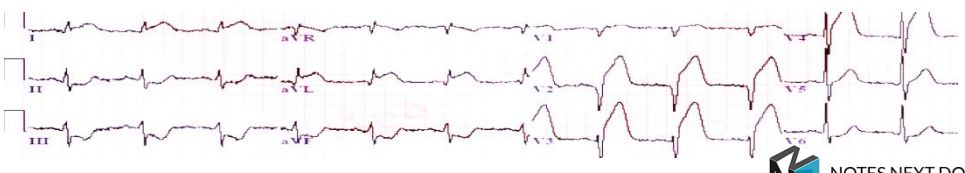
Dual antiplatelet
Aspirin + P2Y12 blocker

Drug eluting stent-
Sirolimus
Immunosuppressant-
mTOR inhibitor

Thrombocytopenia
Hyperlipidemia (TGL)

Paclitaxel

Peripheral neuropathy
Myelosuppression



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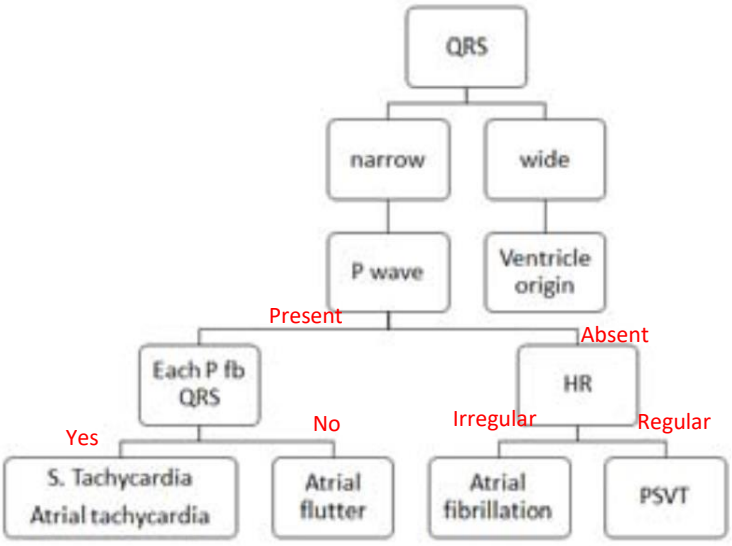
Case: A 21-year-old patient presented with palpitations. Pulse rate 160/min, BP-104/70 mmHg. ECG findings are narrow QRS complex + absent P wave + regular rate. What will be likely diagnosis?

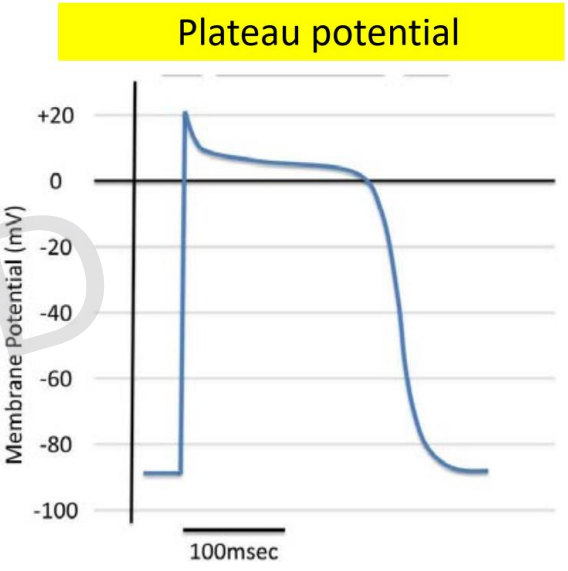
Clinical Approach

- Narrow is <3mm
- Wide is >3mm



Physiology

Plateau Potential



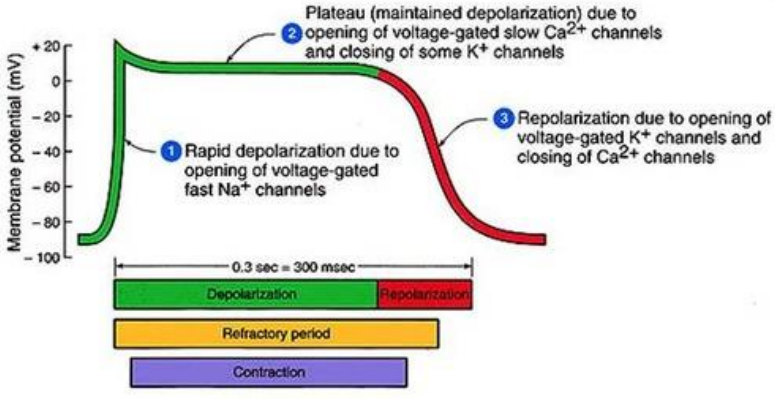
- Phase 0: Depolarization
  d/t opening of Na channels
  Sodium Influx

- Phase 1: Early Repolarization
  d/t **decrease** in Na Influx
  and Increase in Potassium efflux

- Phase 2: Pleateu Phase
  Potassium Efflux = Calcium Influx via slow calcium channels

- Phase 3:
  Only Potassium EFFLUX via a different channel

- Phase 4 : Hyperpolarization



Advantage: Prolongation of the Absolute refractory period (therefore no tetany in the cardiac muscle)

Pacemaker Potential

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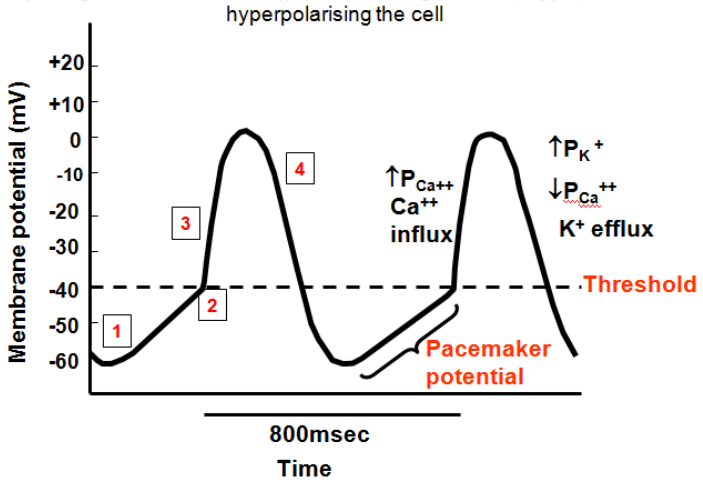
Normal pacemaker: SA Node (because of highest rate of discharge)

1. 'Funny' sodium channels (I_f channels) are open ($\uparrow P_{Na^+}$); and closing K^+ channels.
2. Transient Ca^{2+} (T-type) channels open, pushing the membrane potential to threshold.
3. Long-lasting Ca^{2+} (L-type) channels open, giving rise to the action potential.
4. Opening of K^+ channels, ($\uparrow P_{K^+}$), and closing of Ca^{2+} (L-type) channels, hyperpolarising the cell



- RMP is about -60 mV
- Depolarization is because of Calcium (via Calcium L channels)
- Repolarization is because of Potassium efflux
- Hyperpolarization/Prepotential is slow and spontaneous till firing level due to
    - Decrease in K Efflux
      Decrease in movements of Potassium (accumulation of positive charge inside the cell.
    - Due to FUNNY Channels/F Channels/H Channels (Both **Sodium Influx (dominates)** and Potassium efflux), Net Gain of Positive charge
    - Calcium Influx through calcium T channels

- Increase in sympathetic discharge acts on Beta 1 Receptors which causes more Calcium channels to open → Decreases the Depolarization time → Increase in HR

- Increase in para-sympathetic discharge ↓es the cAMP → ↑es the Depolarization time → Decrease in HR
- Increase in para-sympathetic discharge opens up the **K_{ACH} channels responsible for potassium efflux** → Slope of Phase 4 decreases → Decrease in HR
- Therefore parasympathetic (Resting vagal tone) has more in regulation of HR.

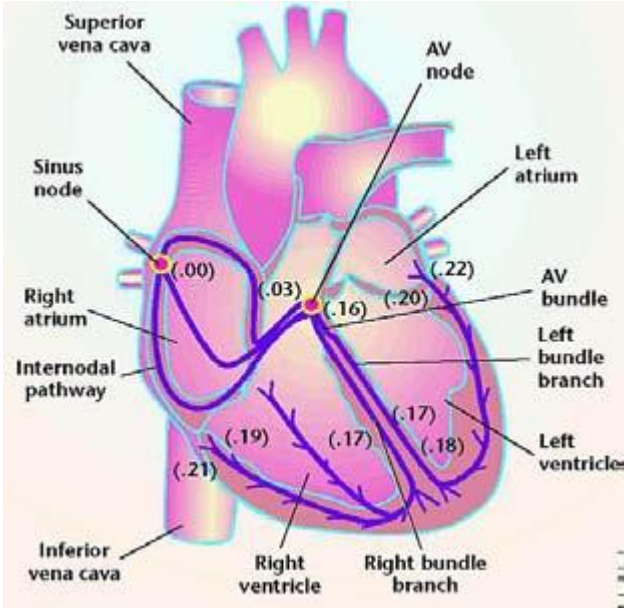
Conduction of Cardiac Impulse

AV Nodal delay:

Reason: 1. AV Nodes fibres are small diameter fibres. 2. They have minimal gap junctions.

Duration of AVN Delay: 92-96 msec (0.1sec)

The impulse in the ventricles spreads in the direction of **endocardium → Epicardium**.



Ventricular Depolarization sequence:

1. Left upper part of IV Septum
   (Septal Depolarization is Left to right)
2. Endocardium
3. Epicardium
4. Base of the heart- epicardium.

Ventricular Repolarization, however, follows opposite sequence.
Epicardium → Endocardium

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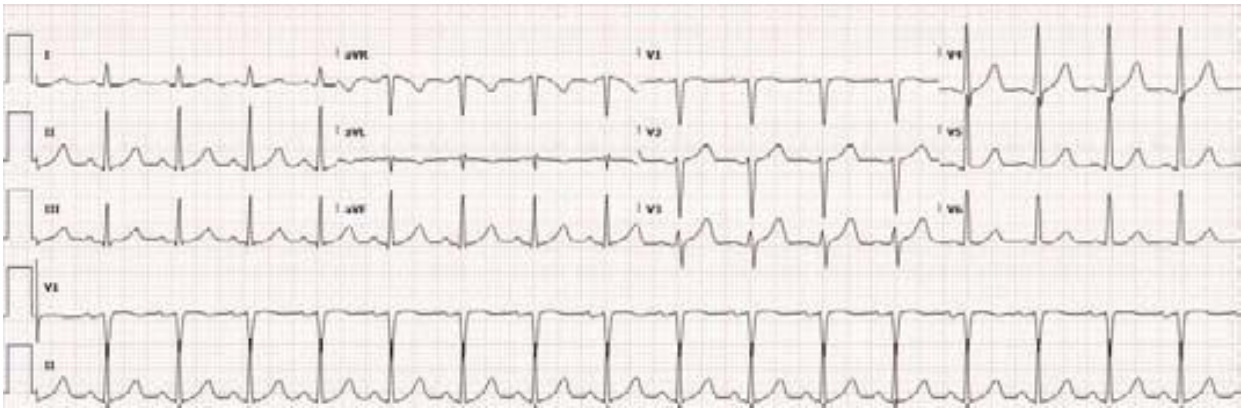
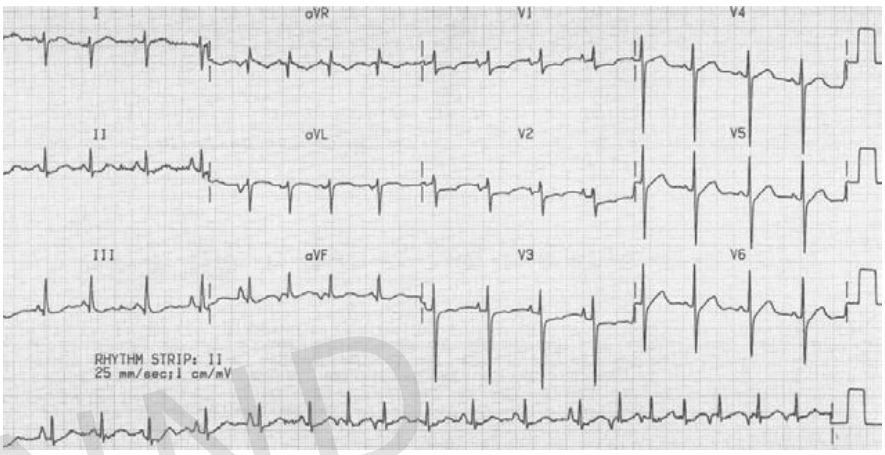
ECG Findings



Lead II : QRS Complex is Normal, P waves are normal. Each P wave is followed by a QRS Complex. Dx: Sinus Tachycardia



Lead II: Narrow QRS Complex, P wave are not normal. There are multiple morphologies of P wave present. (>=3)
Each P wave is followed by a QRS Complex

Dx: Atrial Tachycardia

QRS Complex is <3mm, therefore of supraventricular origin.
P waves are present in 'SAW-TOOTH' pattern. Each P wave is NOT followed by a QRS Complex.
Dx: Atrial FLUTTER

QRS= Normal width.
No definitive P waves.
HR is irregular (Distance b/w any two QRS is changing.
Dx: Atrial FIBRILLATION

NOTES NEXT DOOR

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Lead II: Wide QRS Complexes. Therefore Ventricular origin of tachy-arrythmia.

If HR = 100-250 bpm,
Dx: Ventricular Tachycardia

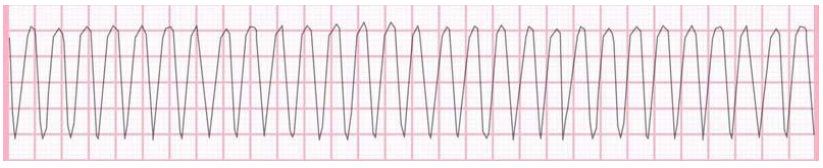
If HR = >250 bpm,
Dx: Ventricular Flutter.

Here Dx: Ventricular Tachycardia.

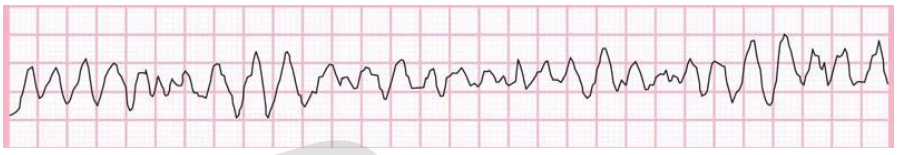
Since all the QRS have same morphology the final diagnosis is **Monomorphic VT.**

Wide QRS Complexes.
HR= 300 bpm.

Dx: **Ventricular Flutter.**

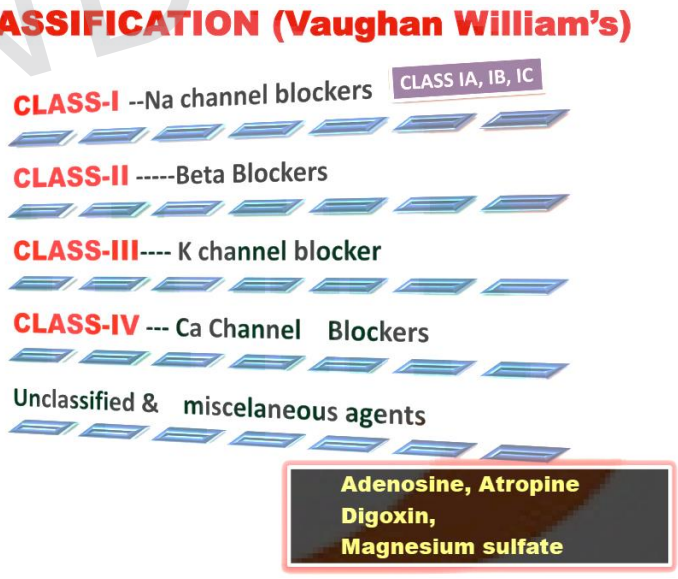


No definitive QRS waves.
Dx: **Ventricular Fibrillation.**



ANTIARRYTHMIC DRUGS

- **Class 1A-** Na Blocking + K Blocking
  - **Eg:** Quinidine, Procainamide & Disopyramide.
  - *Disopyramide has the highest anticholinergic property.*
- **Class 1B-** Mainly Na Blocker, may open the K channels.
  - **Eg:** Lignocain, Phenytoin, Mexiletine, Tocainide.
- **Class 1C:** Only Blocks Na Channels.
  - **Eg:** Flecainide, Propafenone, Encainide, Moricizine.



Class	Mechanism	Example
II	Beta Blockers	METOPROLOL
III	K channel blockers	AMIODARONE DRONIDARONE SOTOLOL DOFETILIDE IBUTILIDE
IV	Ca channel blockers	VERAPAMIL
Other	Digoxin. Adenosine. MgSO4. Atropine	

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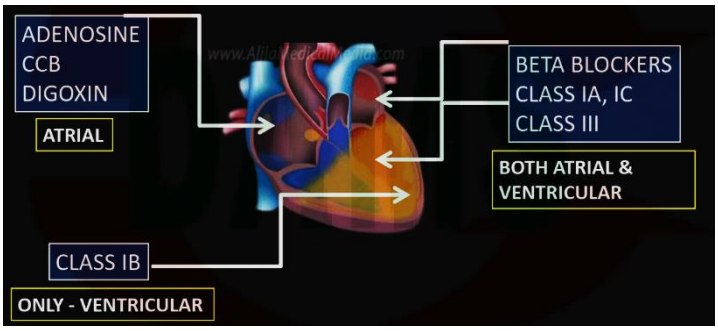

Atrial Fibrillation

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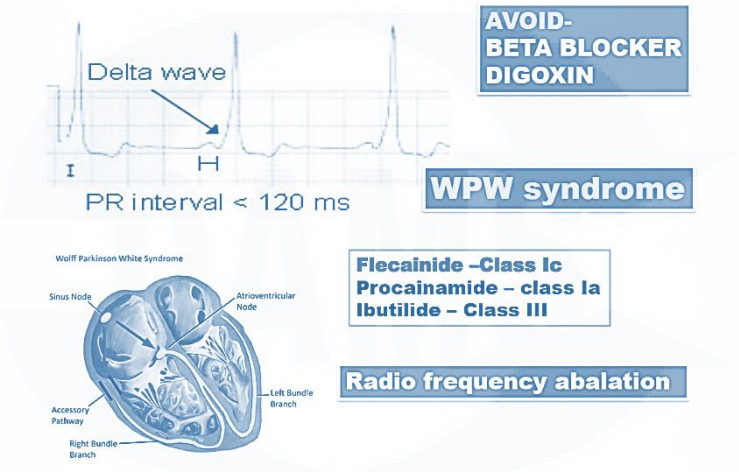
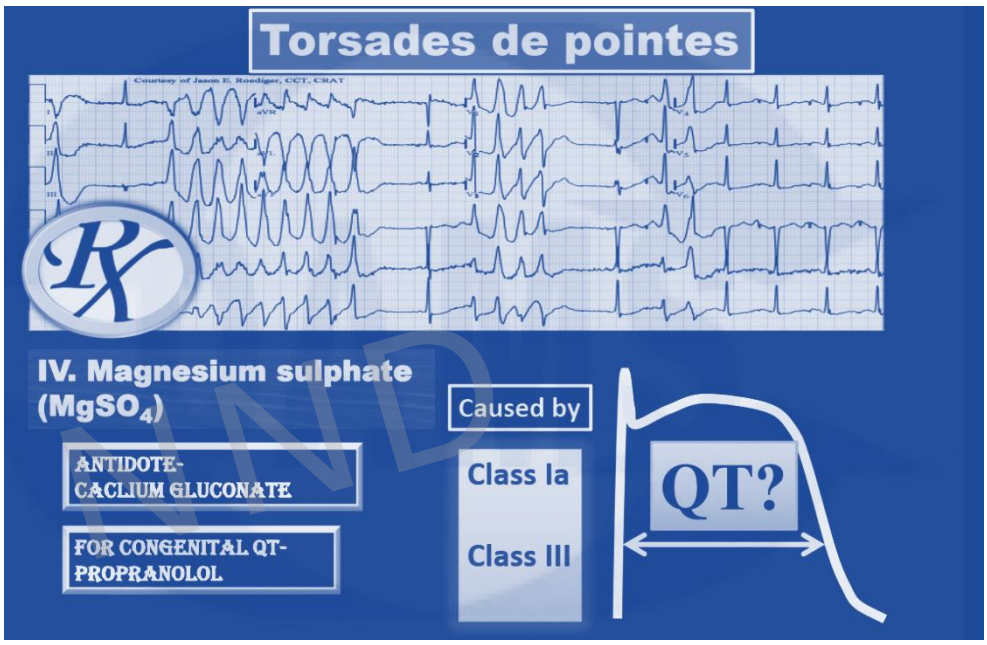
WPW Syndrome



Long QT Prolongation



Atropine is used in:

- Sinus bradycardia
- 1st Degree Heart Block
- 2nd Degree Heart block

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VASCULITIS

Case: A 52-year-old presents with abdominal pain and passage of blood in stools. He was diagnosed of hypertension 1 year back and was put on antihypertensives. Blood examination reveals Creatinine of 2mg/dl, low complement levels negative for ANCA and ANA. Antibodies to HBSAg are positive.

Disease	Vessels involved	Clinical features	Biopsy findings	Other Features
Giant Cell arteritis	Temporal>Vertebral >Ophthalmic	Head ache, Diplopia, blindness, Jaw claudication Age >50	Giant cells Granulomas	Type IV HSR
Takayasu arteritis	Aortic arch, subclavian a	Absent UL pulses, Hand claudication	Giant cells Granulomas	Type IV HSR
Polyarteritis nodosa	Renal>coronary> hepati>GIT **Pulmonary spared**	Hypertension, abdominal pain, GI bleeding, myalgia	Inflammation Fibrinoid necrosis	Type III HSR (HBSAg)
Kawasaki disease	Coronary	Children, Erythema of Conjunctiva, hand feet, oral cavity, Swelling of feet Lymphadenopathy (Mucocutaneous Lymph node Syndrome)	Inflammation Fibrinoid necrosis	? Viral triggers- T cell Damage
Microscopic polyangiitis	Small vessels of Skin, mucus membrane, Lungs, Heart, Brain, Kidney	Hemoptysis, hematuria, GI bleedings	Fibrinoid necrosis Dead neutrophil in vessel wall (Leucocytoclasia)	P-ANCA
Eosinophilic Granulomatosis with polyangiitis	Small vessels of Skin, mucus membrane, Lung, heart, Brain, Kidney	Purpura, Hematuria, GI bleeding, Asthma, Allergies	Fibrinoid necrosis Dead neutrophil in vessel wall (LEUCOCYTOCLASIA) Granuloma	P-ANCA
Granulomatosis with Polyangitis	Small vessel of skin, mucous membranes , Lung, heart, Brain, Kidney	Pnuemonitis, sinusitis, haematuria (RPGN type3)	Fibrinoid necrosis Dead neutrophil in vessel wall (LEUCOCYTOCLASIA) Granuloma	C-ANCE (Vasculitis) T cell mediated granuloma

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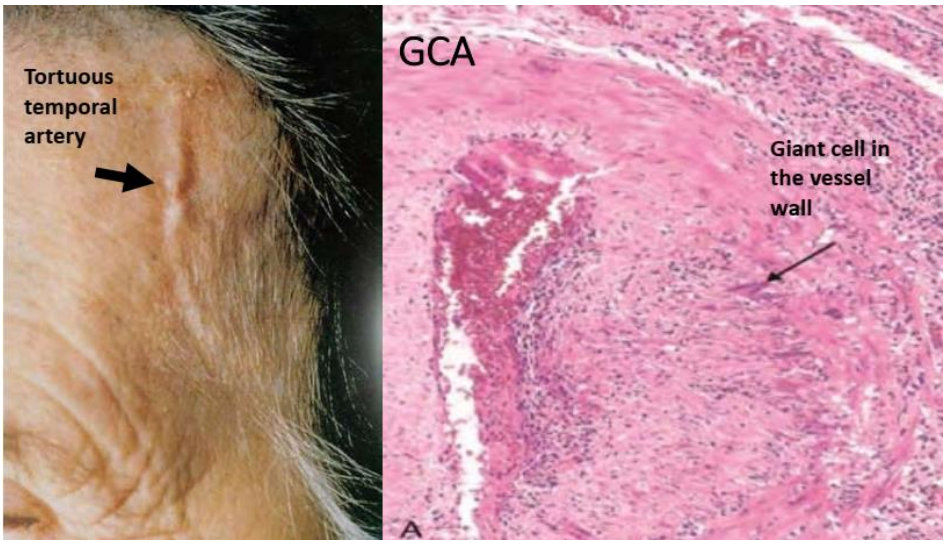
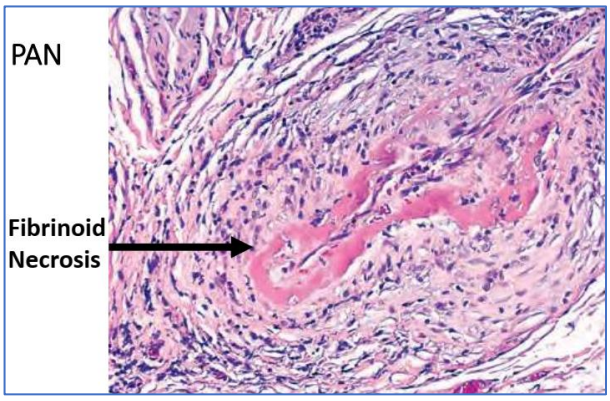
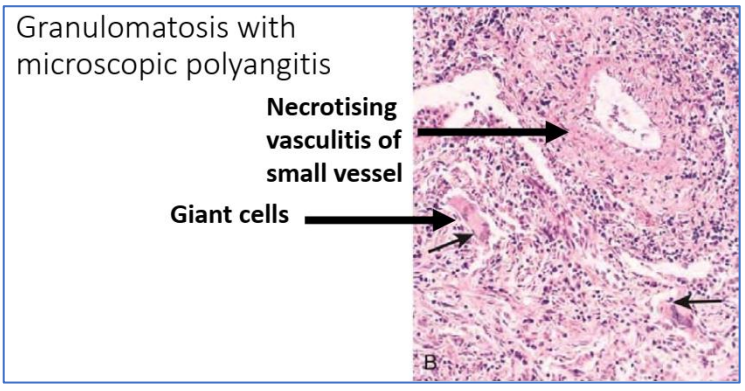


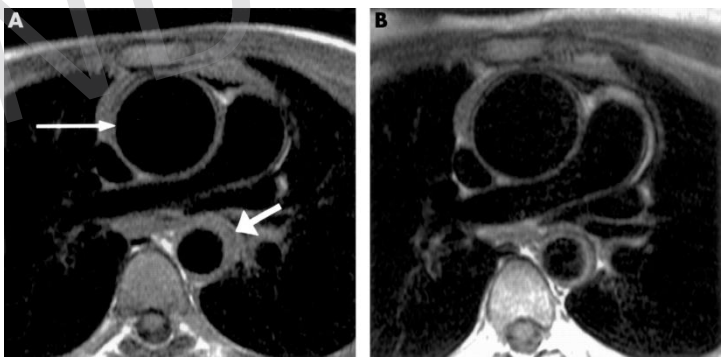




MR Angiogram showing

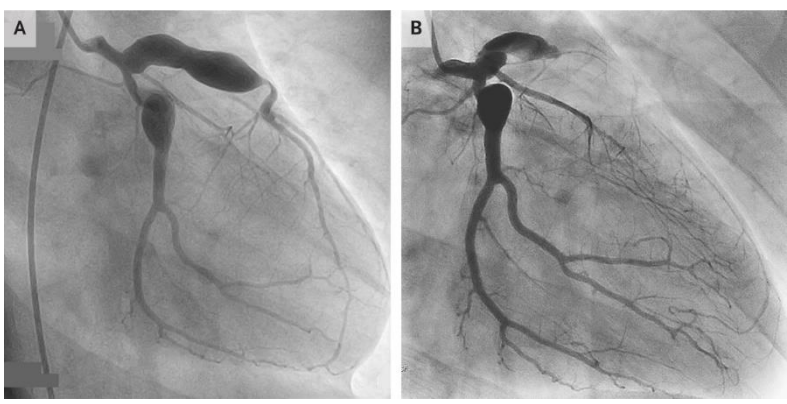
- Vessel Wall thickening in Aorta
- Enhancement

Dx: Aorta Arteritis.



Coronary angiography

Dx: Kawasaki Disease



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Metabolism and IEMs

Glycogen storage diseases

• **Muscles not affected**: GSD type I (von Gierkes) and VI (Hers)
• Hypoglycaemia? = yes
• hepatomegaly? = yes
• lactic acidosis and ketonemia and ***Hyperuricemia***
Yes →Type I dis (*normal structure of glycogen* and *kidneys also affected*)
NO ? → limit dextrin (short outer branches) accumulation →**III GSD (CORI)**
NO? → amylopectin (less branched) or polyglucan body accumulation → **IV GSD(Andersan's)**

• **Glucagon challenge test negative?**
In both fasting and fed? → I
In fasting but not in fed? →III
Progressive liver failure: III and IV

- **Muscles affected ?**
- • Yes? : II(POMPE), V(McARDLE), VII(TARUI)
- Cardiomegaly ? Neonatal Hypotonia? Intra-lysosomal glycogen? : **II**
- Exercise intolerance and pathognomic second wind phenomenon: **V**
- Exercise intolerance with haemolysis: **VII** (no Second wind phenomenon: use of extra muscular fuel)
- No rise in lactate after exercise : V, VII

IEM of Carbohydrate metabolism

1) **Hereditary fructose intolerance: aldolase B deficiency**
Child: **6 month** was normal till breast feeding
Weaning→ fruit juice or sucrose →fructose →F1P →block in pathway
Phosphate sequestration as F1P accumulate → **Hypoglycaemia** (irritability and convulsions).
Why?
1) F1P inhibit phosphorylase competitively
2) Decline in phosphate levels lead to decreased phosphorylase activity.
3) Low ATP (Pi) leads to liver failure (*jaundice and hepatomegaly*) and inhibition of gluconeogenesis and consequent **lactic acidosis**.
TEST : urine gas chromatography or M.S. (**GC-MS**), benedict and seliwanoff positive & negative glucose oxidase test.

2) **CLASSICAL GALACTOSEMIA**

- Enzyme deficient: Galactose 1 phosphate uridyl transferase (GALT)
- *A full term new born child develop jaundice and hepatomegaly on day 4, with vomiting after breast feed. Later on develops oil drop cataract*.

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- Milk has lactose /galactose which cannot be metabolized. (Rx-soy based diet)
- Gal→ Gal1P→ Block →trapping inorganic phosphate as Gal -1- P, leading to ATP depletion and cellular dysfunction (e.g. Liver failure).
- Gal 1P accumulate which inhibit galactokinase . Galactose accumulate and converts into galactitol (osmotic) by *aldose reductase*.
- **Other classical features**: *E coli sepsis*, mental retardation and premature ovarianfailure with unaffected male gonads.

Lab test: deranged LFT, raised *direct bilirubin*, benedict test +, negative glucose oxidase test, Urine GC/MS for galactose.

Galactokinase (GALK) deficiency	**UDP galactose-4-epimerase (GALE) deficiency**
(1st step): *normal growth, cataract which regress with dietary management*. Pseudotumor cerebri (rare).	Same as GALT deficiency with additional ***hypotonia and sensorineural deafness***. As epimerase is deficient diet should be **Gal restricted** not free of Gal→as neural tissues are rich in galactose.

Peroxisomal Disorders

Disorders of peroxisome biogenesis	Single gene/ enzyme defect
Zellweger's spectrum disorders: which include the following -Zellweger syndrome -Neonatal adrenoleukodystrophy (ALD) -Infantile Refsum disease	-X-linked adrenoleukodystrophy - Adult Refsum disease

- Peroxisomes are site of synthesis of Ether lipids which are Plasmelogens
- Peroxins (or peroxisomal/peroxisome biogenesis factors) represent several protein families found in peroxisomes. Deficiencies are associated with several peroxisomal disorders.
- Addl Function of Peroxisome: Degradation of LCFA (Longer than DHA)
- **Adult Refsum Ds** is the defect in α-oxidation of phytanic acid (branched beta carbon)

- Laboratory Findings Common to all **Zellweger Spectrum Disorders**
- Absent Peroxisomes or significantly reduced in numbers
- Catalase in cytosol
- Deficient synthesis and reduced tissue levels of plasmalogens.
- Defective oxidation and abnormal accumulation of *very-long-chain fatty acids* and *phytanic acid.*
- Defects in certain steps of bile acid formation and accumulation of bile acid intermediates.

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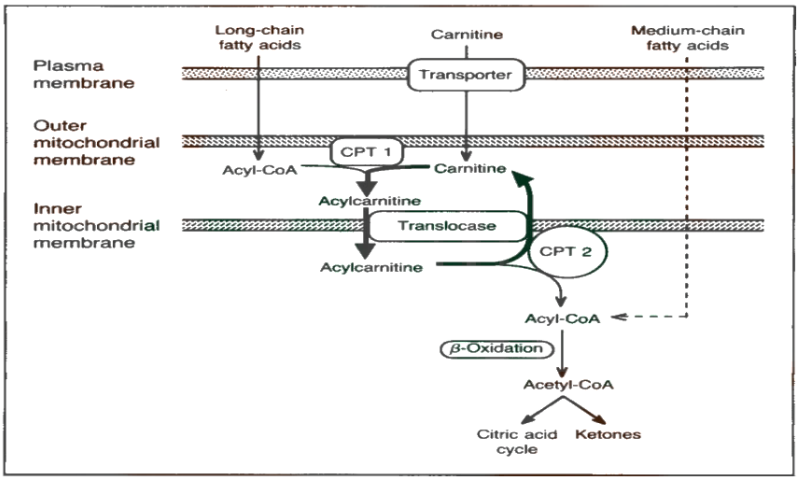
Lipid Metabolism

Beta oxidation of lipids

- Site: Liver
- Carnitine is required for transport of LCFA
- CPT: Carnitine Palmitoyl-transferase



Beta oxidation disorders

• Beta oxidation of FA in mitochondria provides energy in fasting and for gluconeogenesis.
• CPT1 is rate limiting step regulated by malonyl coenzyme A in fed state

Presentation?

• *Hypoketotic Hypoglycaemia* associated with illness, which may progress to cardiomyopathy, hepatic dysfunction (clinically similar to Reye syndrome) with hyperammonaemia and sudden death.

Diagnosis?

• Urine dicarboxylic acids (derived from omega oxidation) and Acylcarnitine abnormalities can detect the abnormalities.

1)MCAD deficiency: *elevated C6 to C10 carnitines*
2)CPT1 deficiency: elevated free carnitine
3)CPT2 deficiency :elevated acylcarnitine

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HYPERLIPIDEMIA- Fredrickson's classification

	Type 1	Type II (a)	Type III
Defect	**Lipoprotein lipase** or its coenzyme **CII** deficiency	**LDL receptor deficiency**	Mutant apo E or **E2** allele expression E3 is normal population E4 : increased risk of Alzheimer's disease
Lipid profile	High Chylomicrons ♣ **TG>1000 mg/dl** ♣ Normal Cholesterol ♣ *Creamy layer of chylomicrons in plasma*	• High cholesterol levels >800mg/dl • Normal TG	• TG and Chol raised almost same levels (>300mg/dl) • Remnants of CM and VLDL accumulate **(BROAD BETA DISEASE- appr as increased beta band in electrophoresis)**
Inheritance	AR	**AD (runs in families)**	AR
Clinical features	**Pancreatitis**, Lipaemia retinalis, Eruptive xanthoma. **NO CVD**	Tuberous tendon xanthoma (at *Achilles tendon*). **Premature CVD**	***Palmar crease xanthoma is pathognomic***

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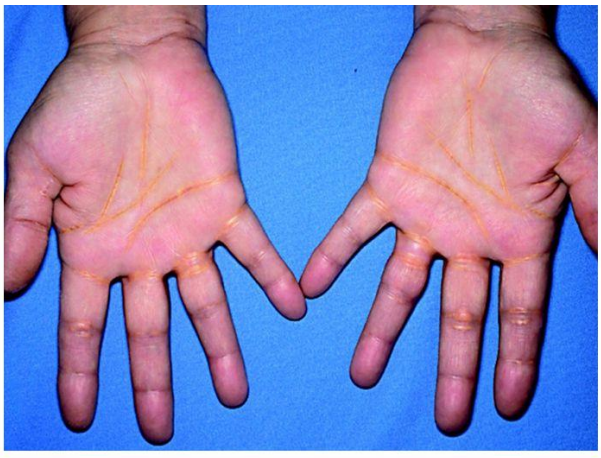
Hyperlipidemia Type 1 indicated by-

Refrigeration Test



•**Xanthoma striata palmaris**: Orange-yellow discolorations of the palmar creases, which in some cases are raised; considered pathognomonic for dysbetalipoproteinemia

Figure1: Bilateral Achilles Tendon Xanthomas

Conditions of low HDL

TANGIERS DISEASE	LCAT DEFICIENCY
• Mutation in gene encoding **ABCA1** • ABCA1 facilitates efflux of unesterified cholesterol from cells to apo **A1.** • **HDL<5mg/dl or absent.** • **Orange tonsils.** • **Low LDL so lo risk of CVD**	• COMPLETE deficiency: NORUM'S DISEASE Low HDL <10mg/dl, **high VLDL (TG)**, *end stage renal failure and haemolytic anaemia.* • PARTIAL deficiency : **FISH EYE DISEASE** Same as above but absent renal failure and haemolytic anaemia. • BOTH conditions present with progressive ***corneal opacification*** due to deposition of cholesterol in cornea (at limbus, so appear as senile arcus)

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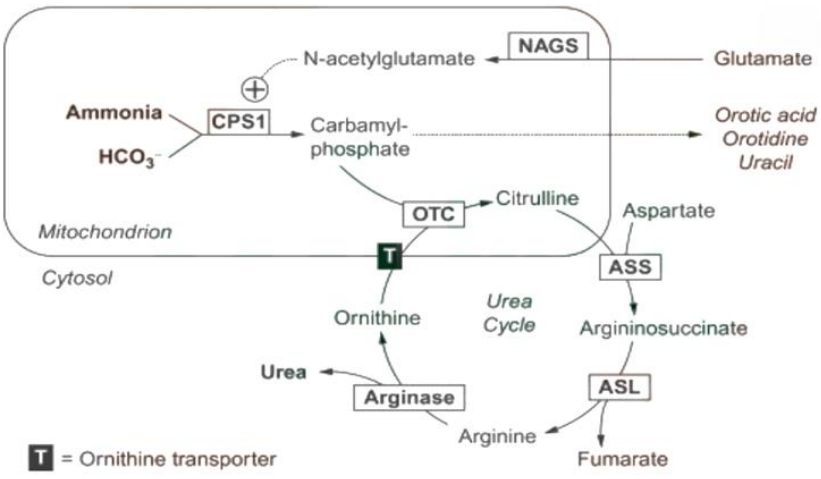
Urea Cycle disorders

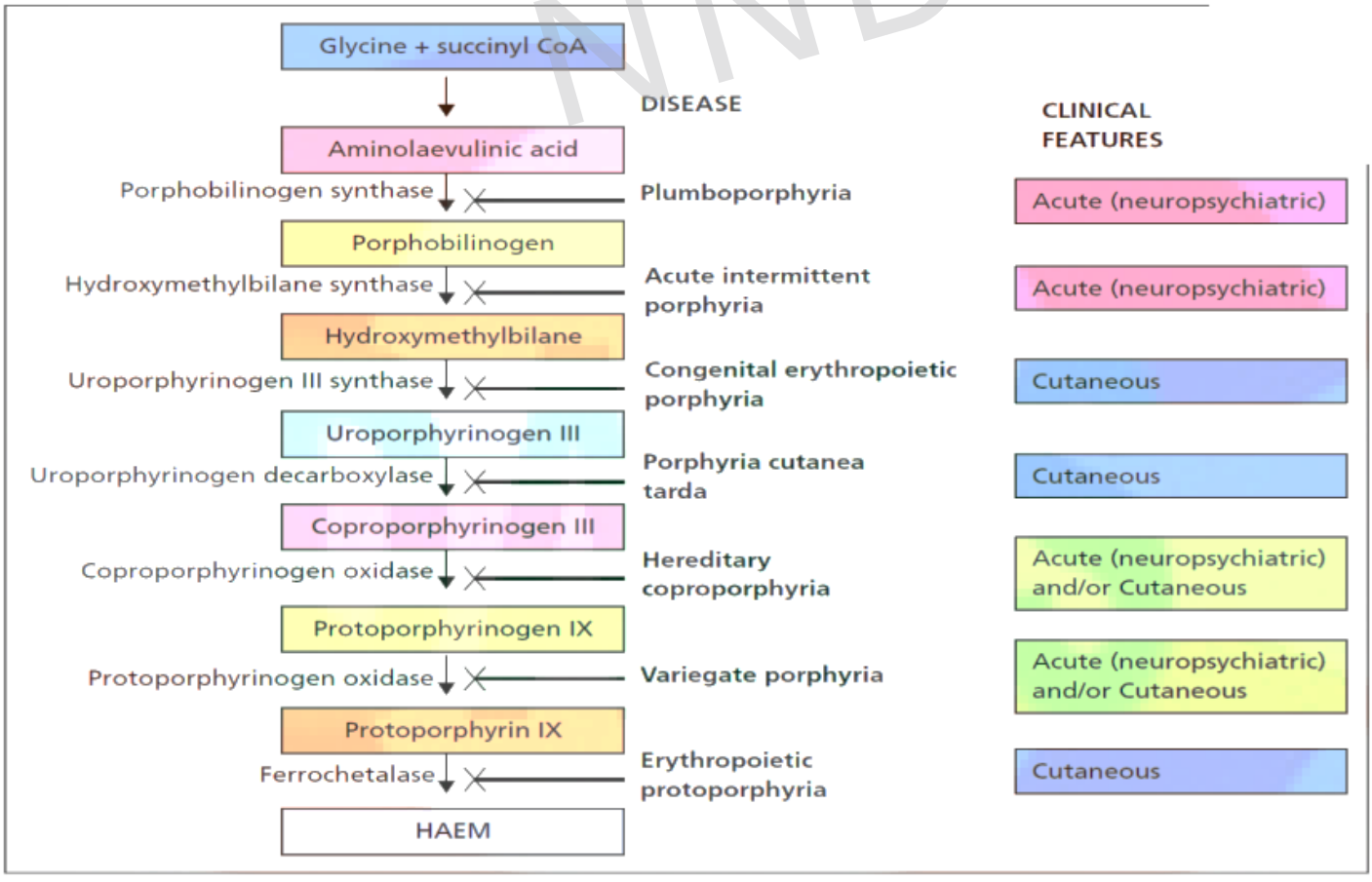
- Suspected UCD: hyperammonemia (High Glutamine) with normal glucose levels and blood pH (may be **alkalosis** but no acidosis)

- 1st step : check CITRULLINE levels



High? Then check arginosuccinic acid level		Low? Then check OROTIC acid levels	
Elevated?	**Absent?**	**HIGH?**	**LOW?**
Arginosuccinic aciduria (ASL deficiency)	Citrullinemia (ASS deficiency)	OTC deficiency/ Type 2 hyperammonaemia	CPS1 deficiency / Type 1 hyperammonaemia

Porphyrias



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- Clinical suspicion of porphyria (drug history) → acute neurovisceral symptoms like abdominal pain and hallucination→ Test urine and faeces for porphyrins

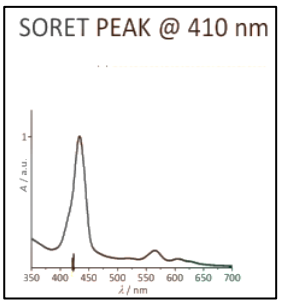
❖Urine PBG increased but faeces negative for porphyrins→ Acute intermittent porphyria (no photosensitivity).

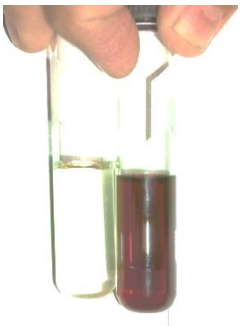
❖**Soret band**: absorption peak at 410 nm by spectrophotometric analysis of urine . Urine is wine colored.

❖Urine (raised PBG) and faeces both positive for porphyrins

Faeces has mostly coproporphyrins III→ Hereditary **coproporphyria**

Faeces has **protoporphyrins** and coproporphyrins→ **Variegate porphyria**





- **Cutaneous photosensitivity**? But no acute clinical features

❖Increased urinary uroporphyrinogen I and coproporphyrinogen I → congenital erythropoietic porphyria(CEP)(**erythrodontia**)

❖Increased erythrocytic protoporphyrin→ Erythropoietic protoporphyria (EPP)

❖Active cutaneous porphyrias can be diagnosed as a first step by ***fluorescence emission spectroscopy*** screen in a freshly separated plasma sample. Mostly fluoresce at **610 to 640 nm**.

❖**Lead** exposure inhibit ALA dehydratase and **increases urinary ALA**.

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Disorders of Purine Salvage Pathway

Lesch Nyhan Syndrome

- **X-linked** recessive disorder.
- Brain (particularly Basal ganglia/Dopaminergic neurons) is major site of purine salvage.
- **Complete deficiency** of the enzyme, hypoxanthine-guanine phosphoribosyl transferase (**HGPRT**).
- Characterized by **hyperuricemia** (WHY? → PRPP accumulation which activate Rate limiting step of purine synthesis) *to which mothers may describe **yellow**- **orange crystals** or grains in the diapers.*
- Severe action dystonia, choreoathetosis, ballismus, cognitive and attention deficit or **mental retardation**, and **self-injurious behaviour**.

Other important metabolic conditions associated with hyperuricaemia

1) Overactivity of PRPP synthetase (mutations causing low Km)
2) Glucose 6 phosphatase deficiency (Type 1 GSD)
3) GAL-1-P uridyl transferase deficiency (galactosemia)
4) Aldolase B deficiency (hereditary fructose intolerance)
5) Alcoholism

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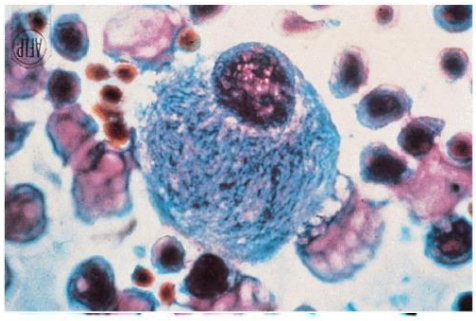
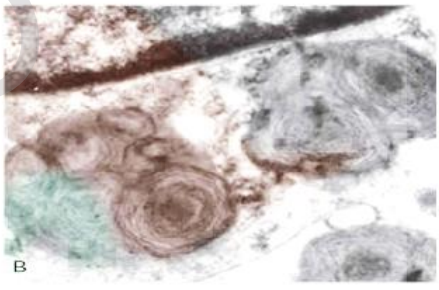
SPHINGOLIPIDOSES

SPHINGOLIPIDOSES	FABRY	GAUCHER	NIEMANN PICK'S	TAY SACH
ENZYME DEFICIENT	α-GALACTOSIDASE -A	Glucocerebrosidase or **β-glucosidase**	**Sphingomyelinase**	β-hexosaminidase A
Deposited material	Ceramide trihexoside	Glucocerebrosides	sphingomyelin in organs mainly in brain and RBC	GM2 ganglioside -Deposition of GM2 **limited to nervous tissue(all cell in sandhoff)**
Clinical feature	**X LINKED-R** Angiokeratoma, acroparaesthesia and corneal verticillate.	**Bone pain/crisis**, hepatosplenomegaly, **Erlenmeyer flask deformity of femur, *pancytopenia*** or (easy bruising).	Cherry red spot in macula and hepatosplenomegaly	Cherry red spot in macula but **no** hepatosplenomegaly
LAB diagnosis	URINE:PROTEINURIA Fat bodies or **mulberry cells** with **Maltese cross** appearance.	Glucocerebroside in macrophage produce **Gaucher cell** which have '**crumpled tissue paper**' appearance	Histopathology ;**foamy macrophage (bubbly appearance)**, Zebra body in inclusions.	Biopsy :' **onion skinning' of lysosomes**

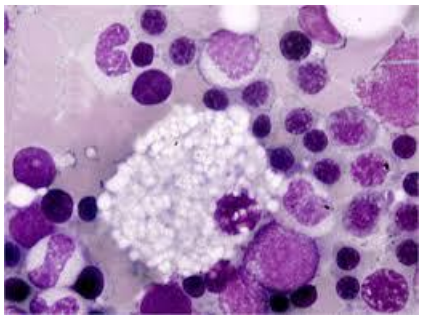
Gauchers disease :wrinkled or crumpled tissue paper appearance of histiocytes



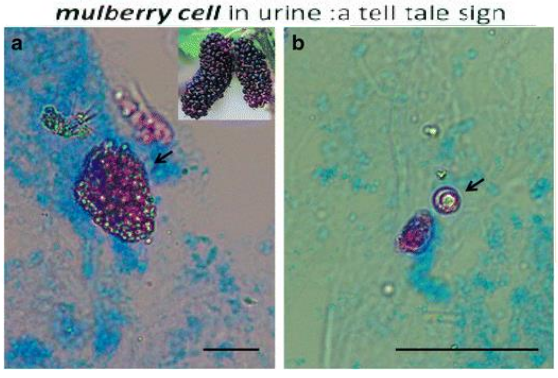
Tay sach disease: lysosomes with onion skin



Niemann pick disease :Foamy histiocytes /foam cell with bubbly appearance



FABRY disease : maltese cross and ***mulberry cell*** in urine :a tell tale sign



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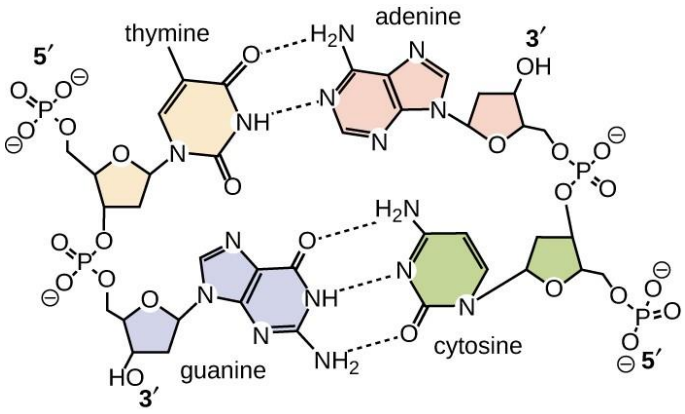
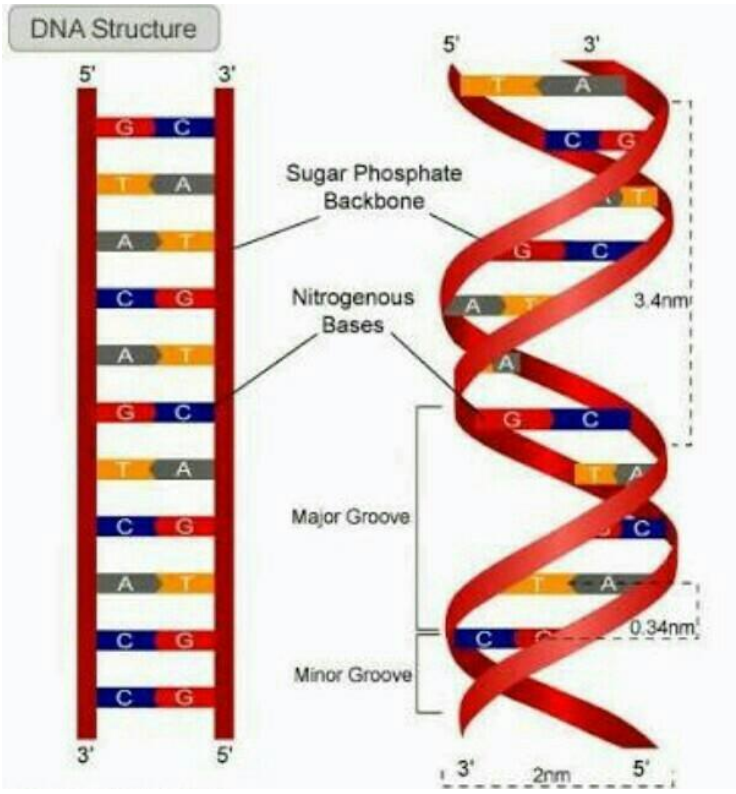
Molecular Biochemistry & Genetics

Watson and Crick Model of DNA

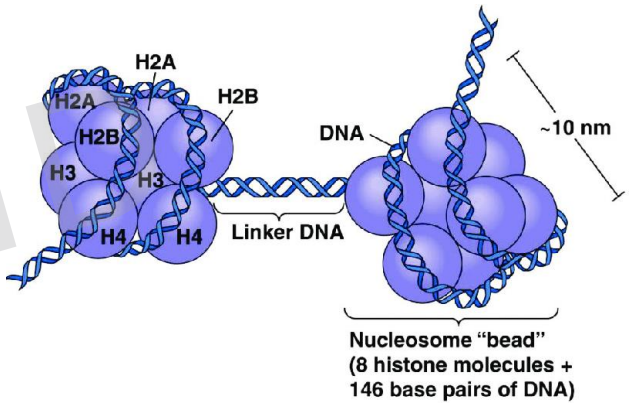
- Proposed in 1953
- Anti-Parallel Double stranded DNA
- Helically coiled along a long axis
- One Helix = 3.4 nm = 34 Armstrong
- One helix has 10 bp
- Each Base pair has distance of 3.4 Å
- Two nucleotides are connected by phosphodiester bonds, where base pair is not a part of these bonds
- A and T have 2 hydrogen bonds in between them
- G and C have 3 hydrogen bonds in between them

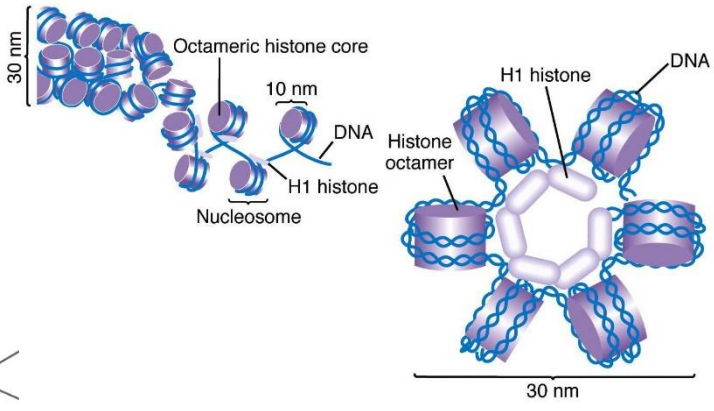




Nucleosome

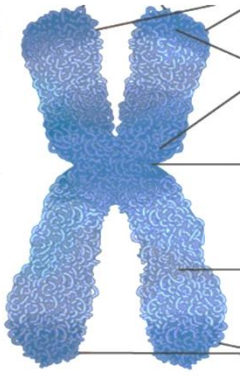
- Histone Octamer
- 1.75 turn of DNA around one ocatmer consisting of total 146 base pairs.
- Linker DNA = 20-90 base pairs
- Polynucleosome: "Pearls or Beads on string" appearance.

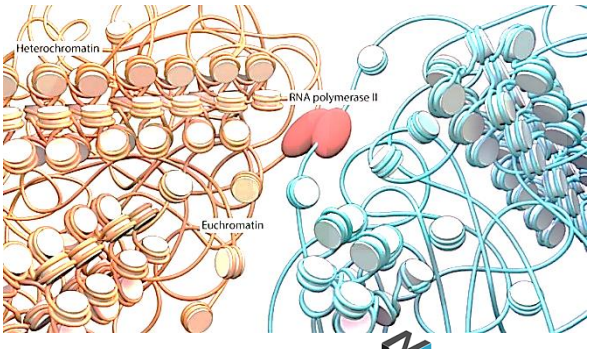




Chromosome Parts:

- Heterochromatin:
  - More condensed
  - Silenced genes (methylated)
  - Gene poor (high AT content)
  - Stains darker
- Euchromatin:
  - Less condensed
  - Gene expressing
  - Gene rich (higher GC content)
  - Stains lighter





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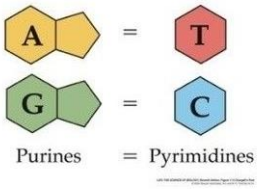
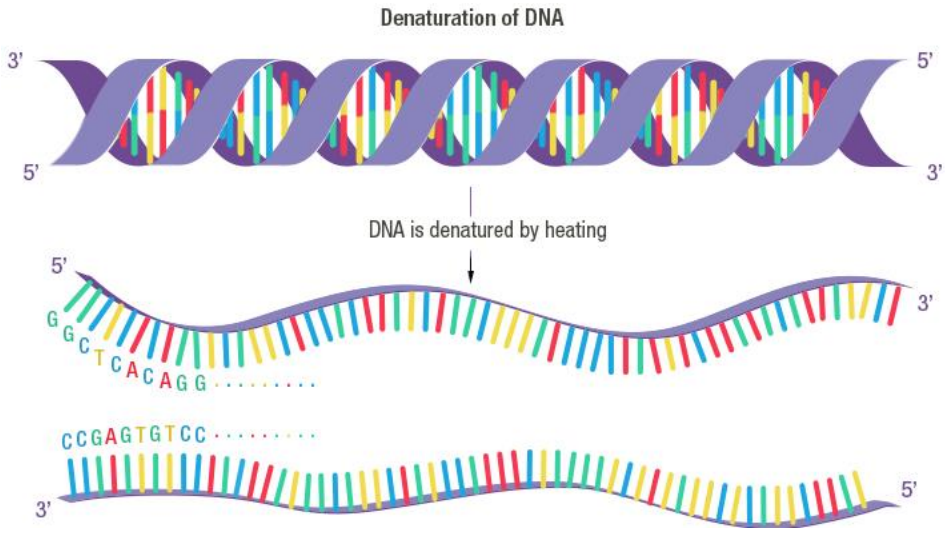
Chargaff's Rule



- Only applicable on ds DNA
- A pairs with T and G pairs with C
- Number of purines is equal to number of pyrimidines
- Ratio of purine bases and pyrimidine bases is one.

- The amount of Adenine = the amount of Thymine.
- The amount of Guanine = the amount of Cytosine.
- He failed to make a connection to the structure of DNA.
- Indicated that DNA is symmetrical.

Denaturation of DNA

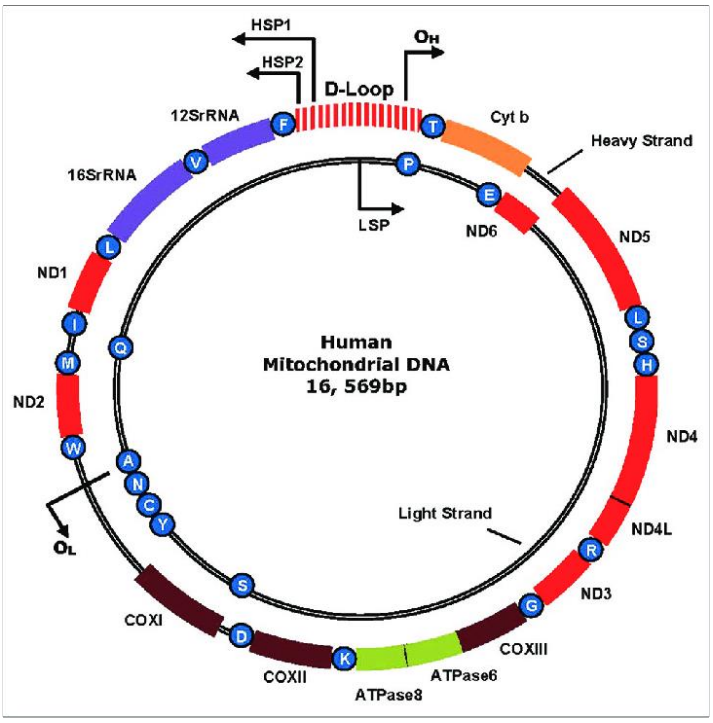


- A/k/a Melting of DNA
- Means that the **hydrogens bonds between the base pairs are broken.**
- Not to confused with denaturation of protein: Loss of 4°, 3° and 2° structure (NOT 1°)
- DNA can be denatured by heating and alkali exposure. (0.5 NaOH)
- Done in PCR or Blotting techniques

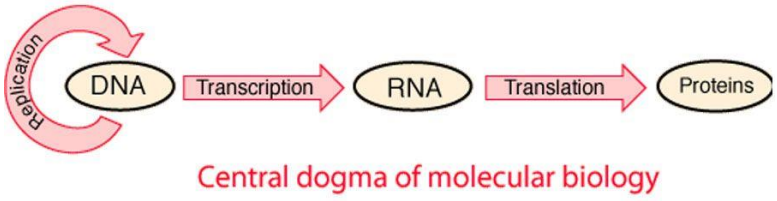
- Strand separation is also known as melting / denaturation of DNA.
- Increasing the temperature or decreasing the salt concentration leads to strand separation.
- Ten-fold increase in monovalent cation increases Tm (melting temperature) by 16.6°C

Human Mitochondrial DNA

• 1% of total cellular DNA lies in the mitochondria
• Consist of 2-10 copies of small circular DNA
• Maternal inheritance (mtDNA absent in sperm)
• Mt DNA codes for 13 protein that play a key role in respiratory chain out of total more than 80 proteins. [13/>80] [<20%]



Central Dogma of Genetics



Central dogma of molecular biology

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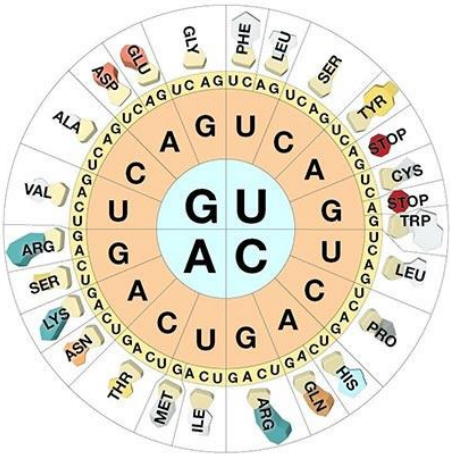
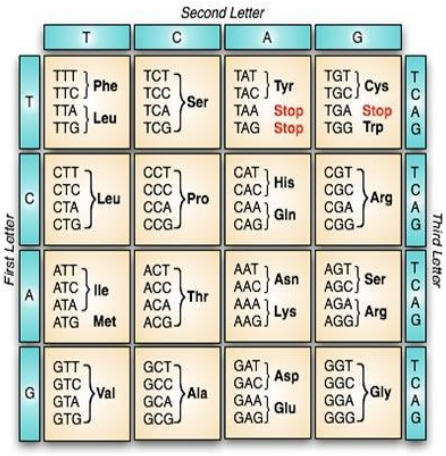
Genetic Code



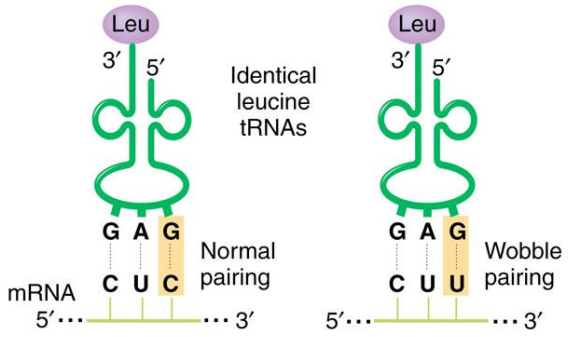


Characteristics

- Codon made up of three nucleotides
- Nonoverlapping
- Codons read continuously
- Degeneracy
- Unambiguous
- Universal(nearly)

61 codons + 3 stop codons

Degeneracy



- Multiple codons for same AA
- Explained by Wobble's hypothesis
- Given by Crick
- Applicable only on 3rd Nt of each codon
- **Max wobble is by T**

Codon Nt at 3'	Codon Nt at 5'
A	U/T
C	G/T
G	C/U
U	A/G/T
T	U/C/A

NND

Exceptions to the rule of universality

Codon	**Cytoplasmic mRNA**	**Mitochondrial mRNA**
UGA	Stop	Tryptophan
AGA	Arginine	Stop
AGG	Arginine	Stop
AUA	Isoleucine	Methionine

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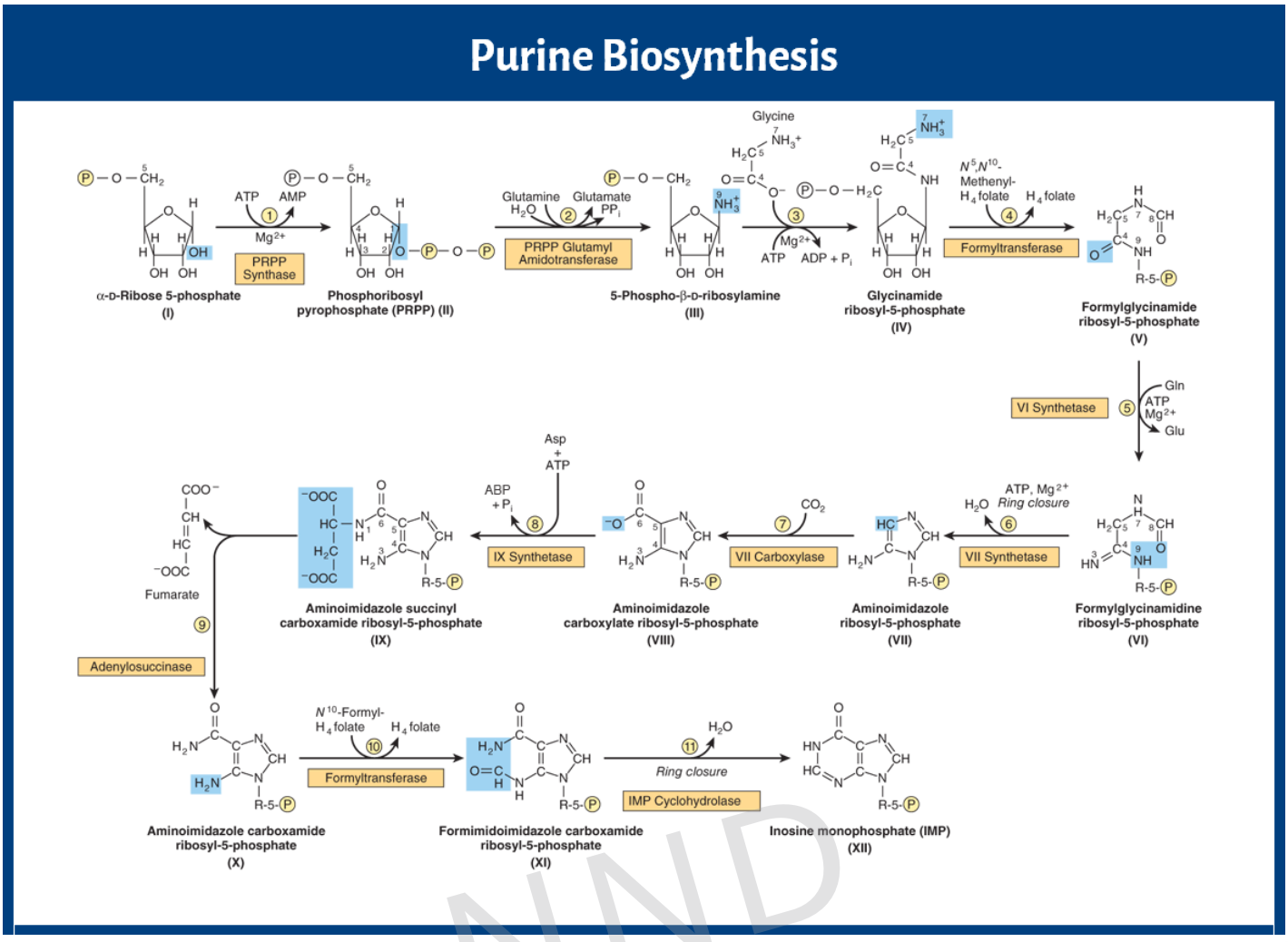
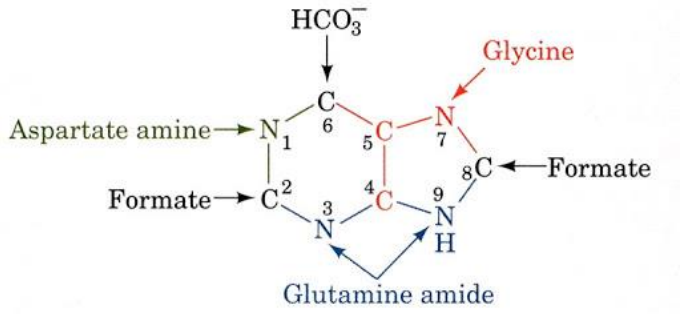
Metabolism of nucleotide



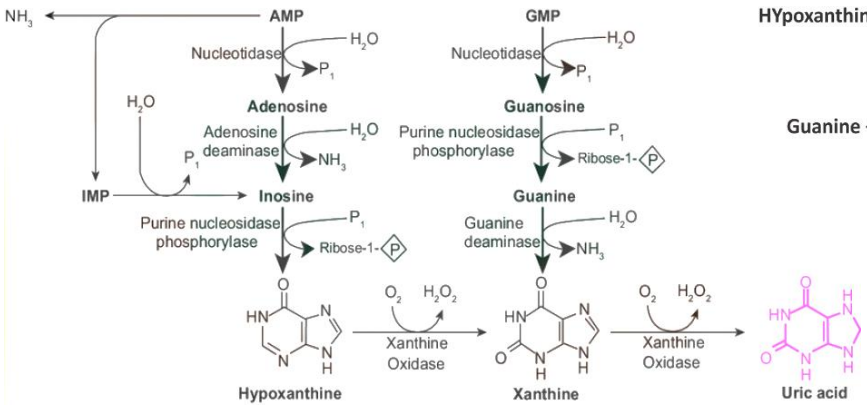
Important points:

- Multi step process
- Takes place in Liver
- Purine ring is formed on PRPP (Phosphoribosyl Pyrophosphate)
- Nitrogen at 1, 3, 7, 9 positions



Salvage pathway for purine nucleotide biosynthesis

- Hypoxanthine-Guanine Phosphoribosyl Transferase is a **bifunctional** enzyme.
- Birds have uricase enzyme metabolizing uric acid further to allantoin (NOT IN HUMANS)



Adenine + PRPP —(Adenine Phosphoribosyl Transferase)→ AMP + pyrophosphate

HYpoxanthine + PRPP —(Hypoxanthine-Guanine Phosphoribosyl Transferase)→ IMP + pyrophosphate

Guanine + PRPP —(Hypoxanthine-Guanine Phosphoribosyl Transferase)→ GMP + pyrophosphate

Adenosine deaminase deficiency is associated with SCID (Severe combined Immune Deficiency) which is a lethal disorder where both T and B cell defunction. Treated by GENE THERAPY

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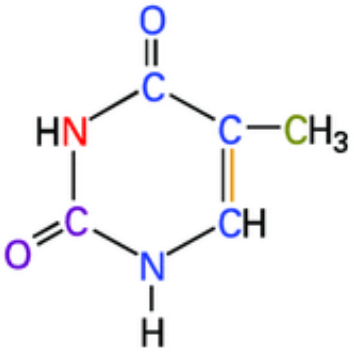
Sources of atoms in Purines vs Pyrimidines

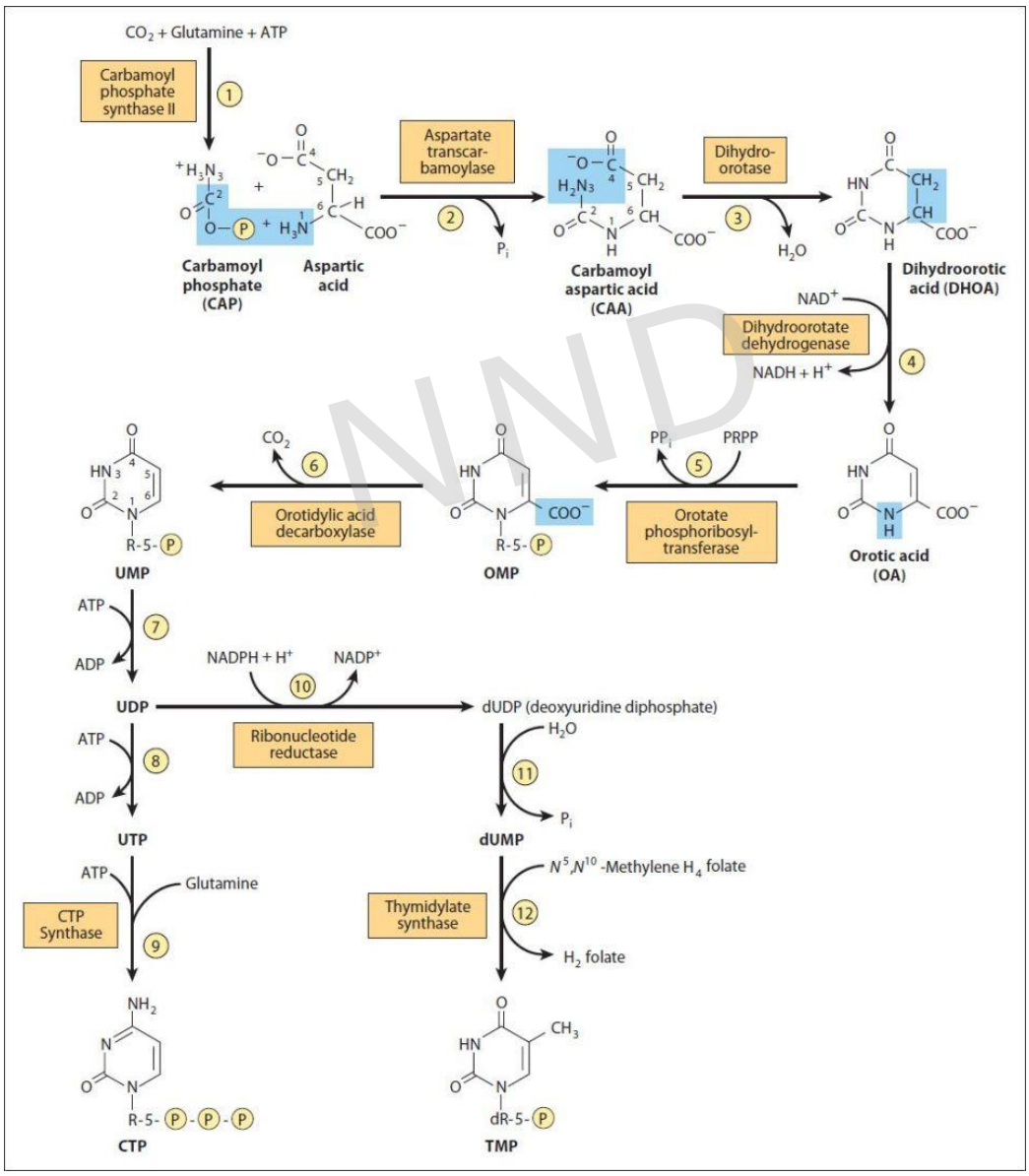
Purine Nucleobases
(Adenine)

Aspartate
Glutamine
Glycine
10-formyl-THF
5,10-methylene-THF
CO_2
HCO_3^-
Ubiquinone/DHODH



Pyrimidine Nucleobases
(Thymine)

Pyrimidine Synthesis



- **Orotic Aciduria:** d/t Deficiency of enzyme present at Step 5 or both Step 5 & 6

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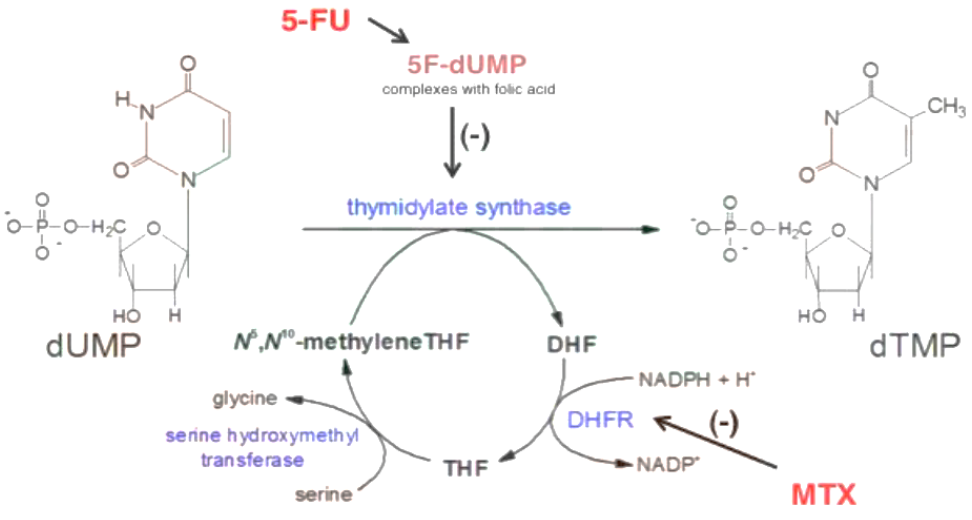
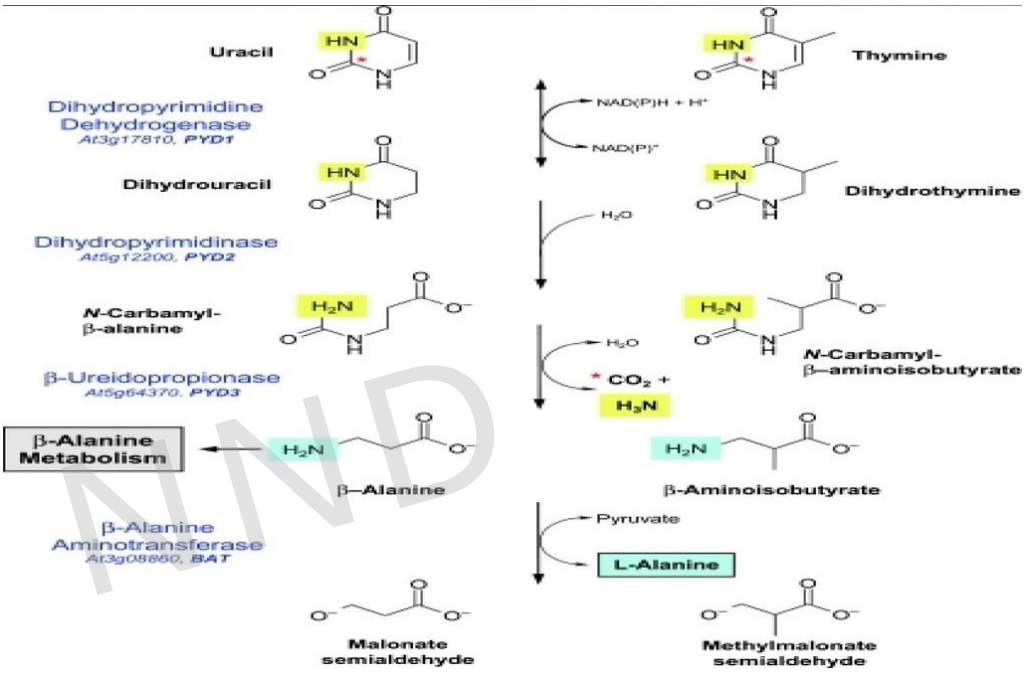
- **dTMP** synthesis is important for formation of DNA.
- This production is inhibited in primary mechanism is chemotherapy in malignancies



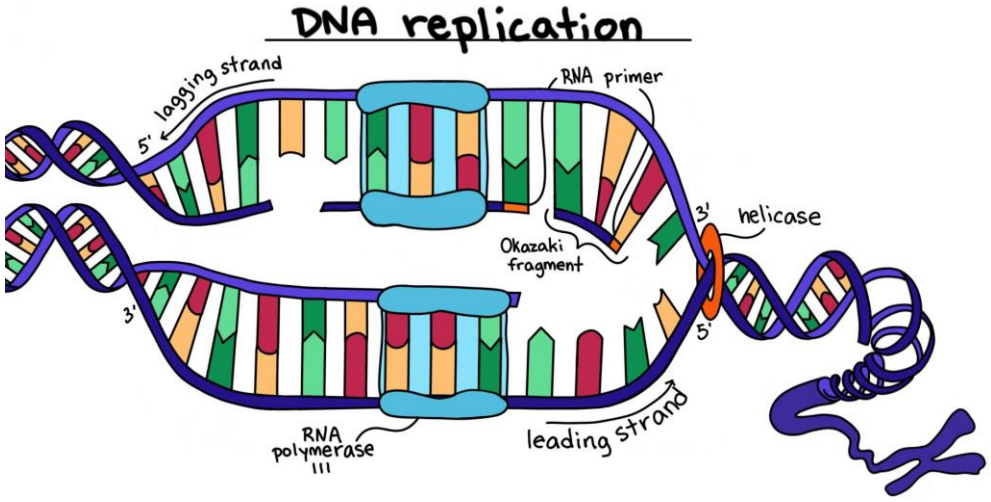
Pyrimidine Catabolism

- All products are water soluble so accumulation pathology
- End product of this cycle is (NOT URIC ACID)
  - **CO2**
  - **NH3**
  - **Beta Alanine**
  - **Beta-aminoisobutyrate**



DNA REPLICATION

- Bi-directional
- Each strand has one continuous fragment on one side and Okazaki fragments on other side.
- Multiple enzymes, most important being DNA polymerase enzyme.



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Prokaryotic and Eukaryotic DNA Polymerase

Prokaryotic DNA-polymerases

Polymerase	Polymerase activity (for all enzymes 5′ → 3′)	Exonuclease activity
DNA polymerase I	Filling if gap after removal RNA primer, DNA repair, removal of RNA primers	5′→3′ and 3′→5′
DNA polymerase II	DNA repair	3′→5′
DNA polymerase III*	Replication, proofreading and editing	3′→5′

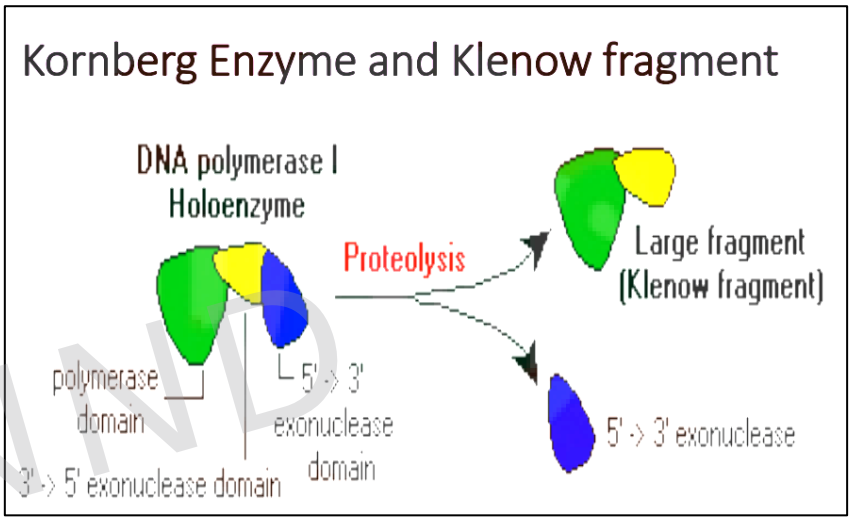
*The main enzyme of replication

70

DNA polymerase [Eukaryote]	Function	Proof reading
Pol α	Primase activity Initiate DNA synthesis	Absent
Pol β	Repair process	Absent
Pol γ	Mitochondrial DNA synthesis	Present
Pol δ	Lagging strand synthesis [Okazaki fragment]	Present
Pol ε	Leading strand synthesis	Present

Kornberg Enzyme and Klenow Fragment

- Kornberg Enzyme is also known as *DNA Polymerase 1*
- Has two fragments, the larger fragment is k/a **Klenow fragment** and has two activities:
  - 5'-3'- polymerase
  - 3'-5' exonuclease



RNA Polymerase

EUKARYOTIC

Gene	Enzyme	Location	Product	Sensitivity to alpha Amanitin (mushroom poison)
I	RNA polymerase I	Nucleolus	**45S pre-rRNA** (5S rRNA + 5.8SrRNA+ 18S rRNA)	Insensitive
II	RNA polymerase II	Nucleoplasm	•mRNA •Most Sn RNA •mi RNA	Very sensitive
III	RNA polymerase III	Nucleoplasm	•5 S rRNA •tRNA •U6 Sn RNA	Moderately sensitive

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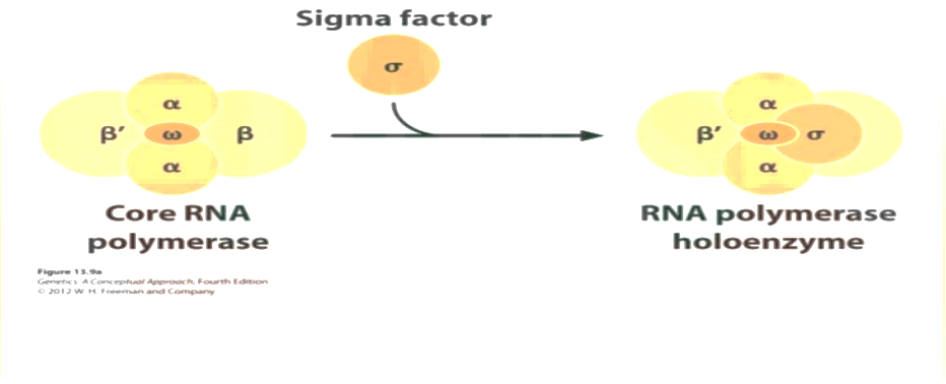
PROKARYOTIC

- Beta subunit is catalytic
- **Sigma subunit is important for recognition of promoter element on the DNA for binding of RNA polymerase enzyme [Foot of RNA polymerase enzyme]**



Post-transcriptional modifications of RNA

(in cases of all- hnRNA (mRNA) , tRNA, rRNA, miRNA)

Post transcriptional Modification of hnRNA (hnRNA to mRNA)

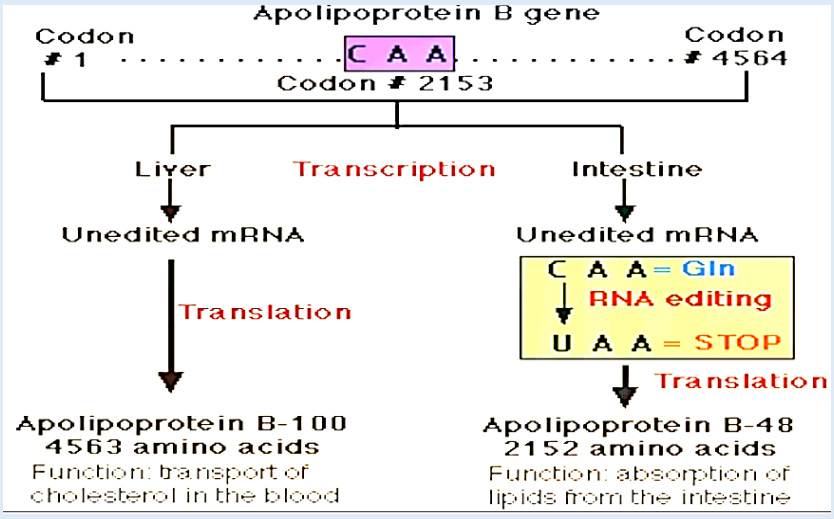
- **Capping at 5'end:**
  Nuclear process
  Transferred by guanylyl transferase [nuclear enzyme]
  Methylation in cytosol by guanine-7-methyltransferase
  Cap is formed by 7-methyl GTP
- **Poly A tail:**
  40-250 adenine nucleotide attached at 3'end
  Polyadenylate polymerase [nuclear enzyme]
- **Splicing:** Via Spliceosome

NND

mRNA Editing

Same gene produces Apo B-48 in intestinal cell and
Apo B-100 in liver cells.
This is due to "mRNA Editing" phenomenon which is seen rarely.

Enzyme responsible in intestine for this phenomenon is **Cytidine Deaminase (Cytosolic)**



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DNA Repair Defect

Defect	Disease
Mismatch	HNPCC
Helicase	Bloom syndrome
Transcription Coupled Repair	Cockayne Syndrome
SS/DS break repair	Breast cancer
Nucleotide Excision Repair	Xeroderma Pigmentosa

Regulator non-coding RNA (ncRNA)- micro & small interfereing

- **miRNA:** Single stranded (produced by double strand precursor), Endogenous
- **si RNA:** Double stranded (endogenous or exogenous)

Both are responsible for KNOCKDOWN of the gene (Down-regulation)

Long Non coding RNA (lncMRA)

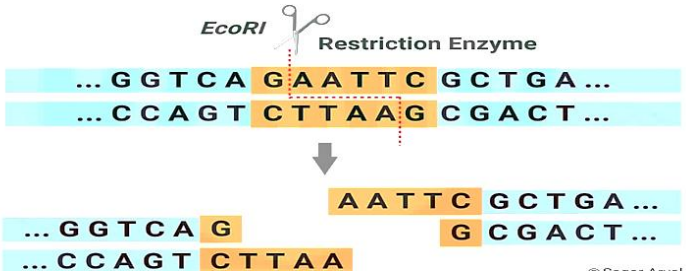
- 300-1000 nucleotide long
- Endogenous
- Contribute in structural aspect of the gene
- Regulation of mRNA gene transcription by RNA polymerase II

NND

Genetic Technologies

RESTRICTION ENDONUCLEASE ENZYME

- Identify palindrome
- May produce blunt or staggered ends
  - "Molecular Scissors"
  - Most Imp- Type II



Type of restriction endonuclease	Site where they cut the DNA
Type I enzymes	cut DNA at random far from their recognition sequences.
Type II enzymes	cut DNA at defined positions close to or within their recognition sequences.
Type III enzymes	They cleave outside of their recognition sequences and require two such sequences in opposite orientations within the same DNA molecule
Type IV enzymes	recognize modified, typically methylated DNA

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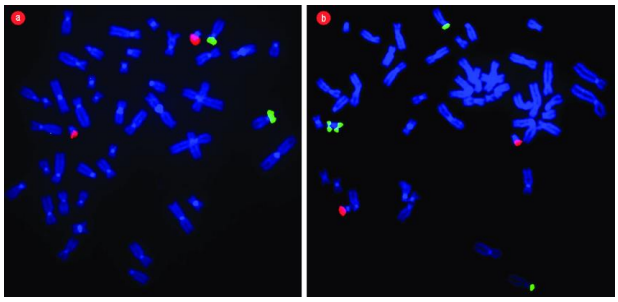
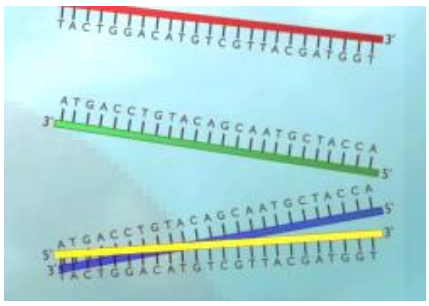
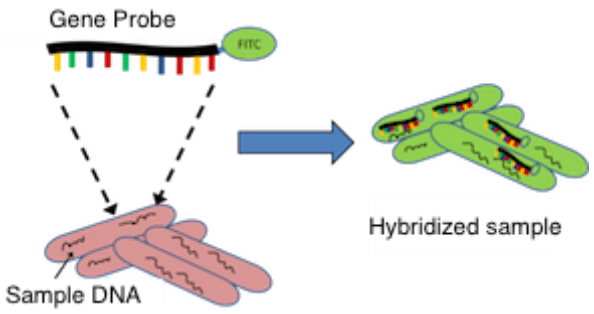
Fluorescence in situ hybridization – FISH



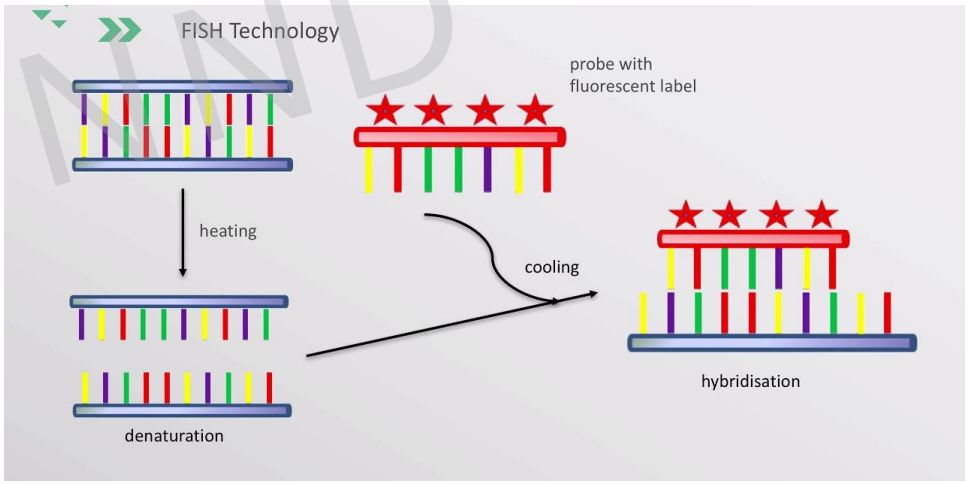
- It is a molecular cytogenetic technique which uses fluorescent probe which is complementary to the specific DNA sequence.
- **Types of probes**
  Centromere probe
  Telomere probe
  Whole chromosome probe
  Locus probe
  Gene detection and localization
  Gene amplification
  Deletion
  Translocation

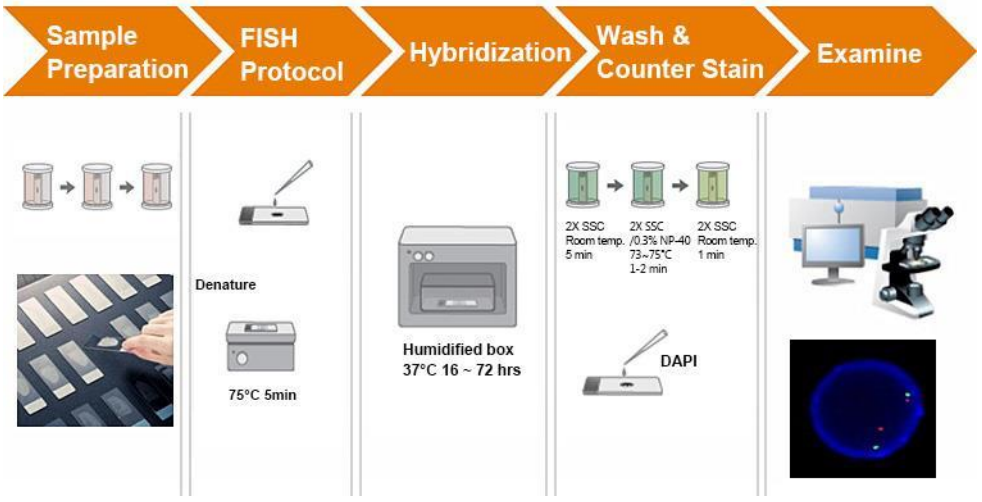


- Probe may be
  - dsDNA probe
  - ssDNA probe
  - RNA Probe
  - Synthetic oligonucleotide probe



- Labelling of the probe:
  - Radioactive
    - 32 P
    - 35S
    - 3H
  - Nonradioactive isotopic
    - Biotin
    - Fluorescent dye
    - Digoxigenin





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Application of FISH

1. **Karyotyping**
   Aneuploidy: Trisomy, Deletion of whole chromosome
   Chromosomal aberration: Deletion, Duplication, Translocation
2. **Developmental biology**
   Gene expression profiling in embryonic tissues

Polymerase Chain Reaction – PCR

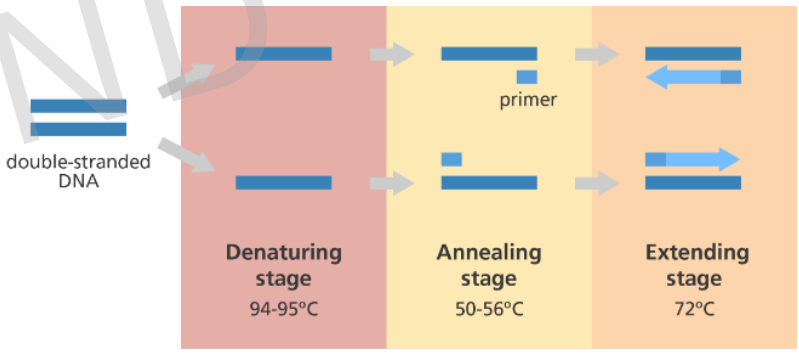
- Introduced by Kary Mullis in 1984
- Based on Target and Flanking sequences.

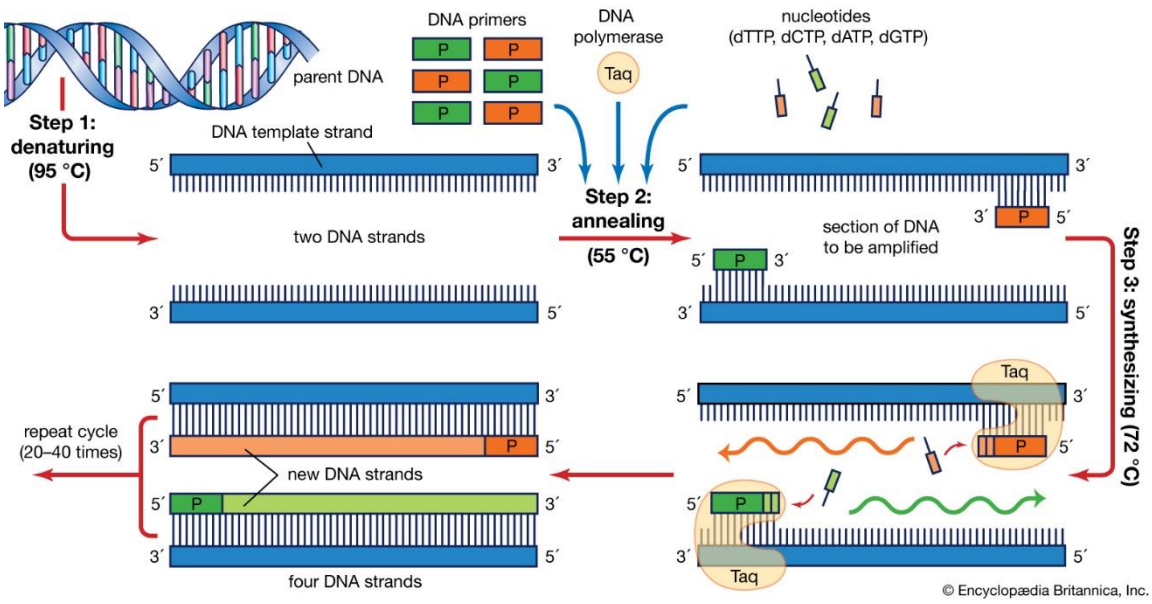
THERMOCYCLER

- Components required are:
  - Target DNA
  - dNTPs (All 4 variety)
  - DNA polymerase(thermostable)
  - Pair of primer (20-30 nucleotide)
  - Magnesium
  - Buffer

- Cycle of PCR

  - Denaturation: 95 degree C x 15 sec
  - Annealing: 54 degree C
  - Elongation: 72 degree C





Application

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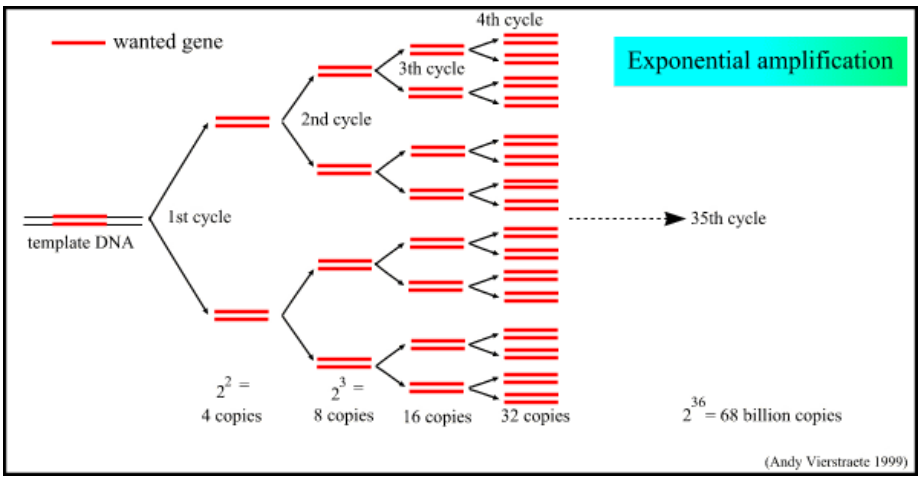
•**In medicine**

detection of bacteria and virus
early detection of cancer
monitor cancer chemotherapy

- **In forensic and legal medicine**
  Parentage dispute
  Criminal case
- **Evolution study**



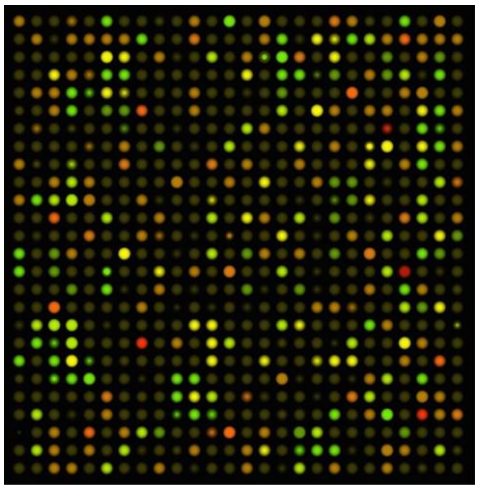
<u>Real Time PCR (qPCR)</u> **NOT RT-PCR**

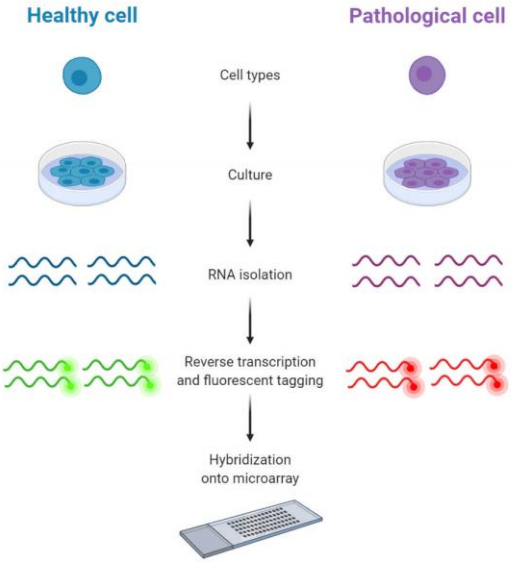
Done for DNA & RNA

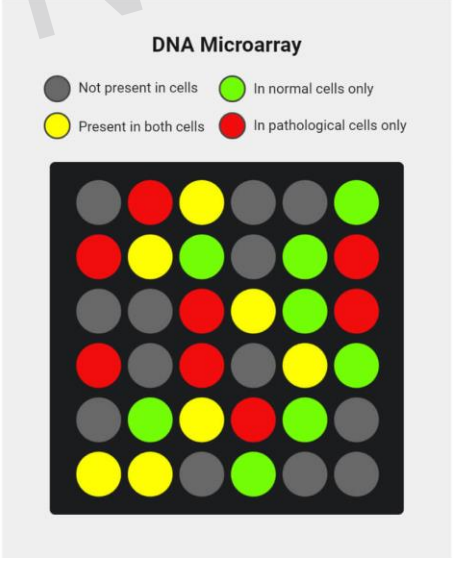
- Done using Dyes like:
  - SYBR Green
  - Taq Mann
  - Molecular Beacons

<u>MicroArray</u>

- Multiple Gene analysis at the same time
- Principle: Hybridization
- Comparison of RNA of two cells







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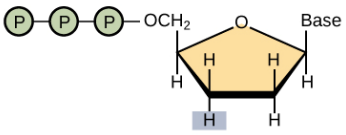
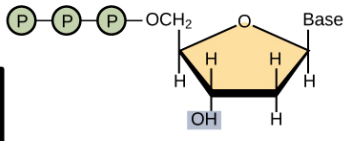
DNA Sequencing by Sanger [di-deoxynucleotide chain termination method]

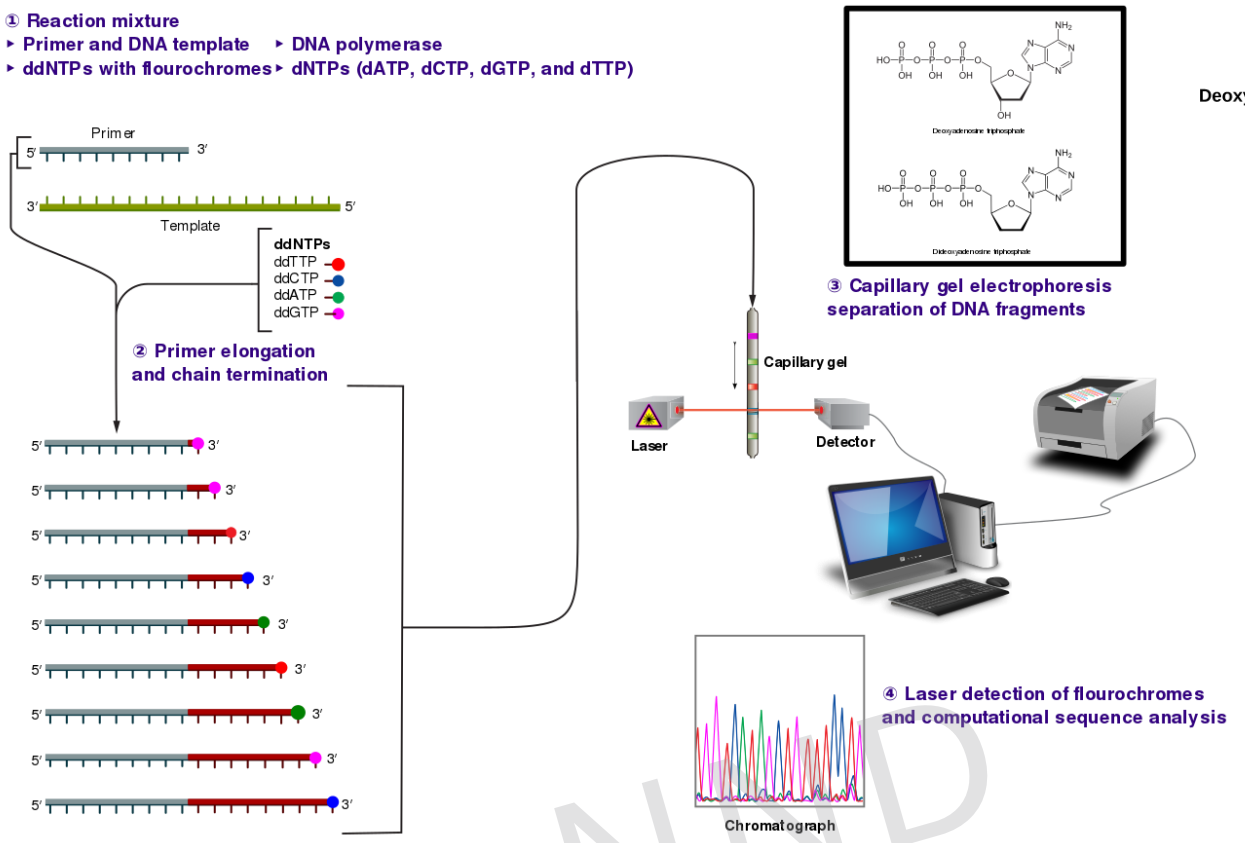


Dideoxynucleotide (ddNTP)

- Enzymatic method
- Uses di-deoxynucleotide
    - Has lack of oxygen at 2nd & 3rd hydroxyl position



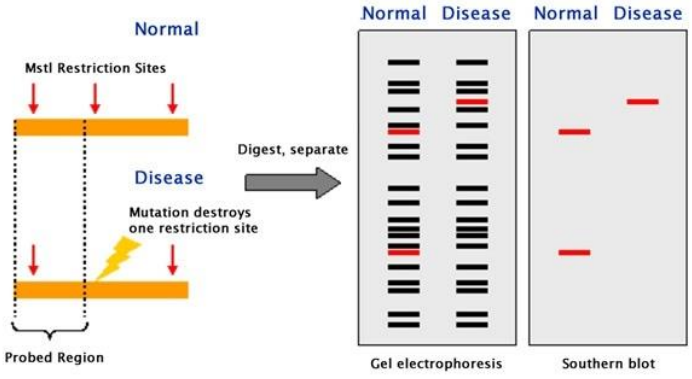
Deoxynucleotide (dNTP)



NND

Restriction fragment length polymorphism

This is based on variation of the restriction site in an individual DNA which may result from polymorphism or mutation.



Polymorphism

It is inherent variability in the sequence of the DNA.

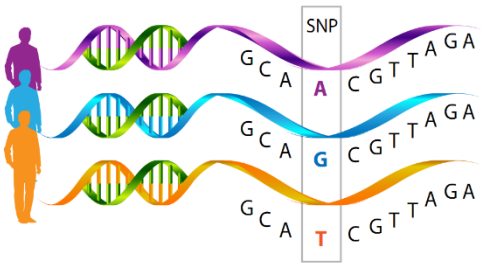
Broadly it is of two types

a) SNP

b) VNTR

i) Mini Satellite

ii) Micro Satellite



SNP technology

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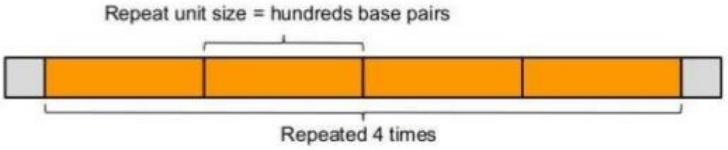
VNTR

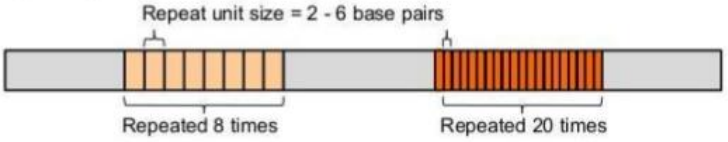
- Variable Number Tandem Repeat (VNTR)
  - sequences that are repeated multiple times and the number of repeats varies from person to person.

Tandem Repeat elements

Minisatellite: Variable Number Tandem Repeats (VNTR)



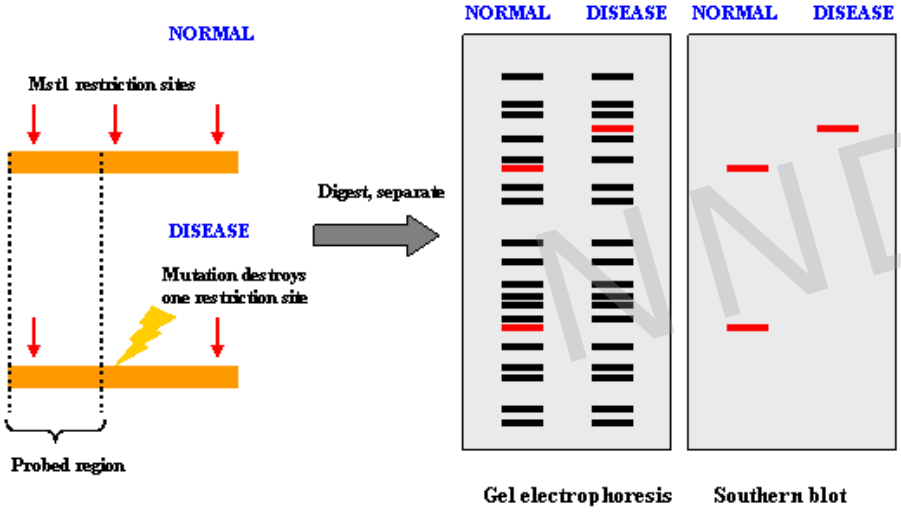
Microsatellite: Short Tandem Repeats (STR) – Simple Sequence Repeats (SSR)



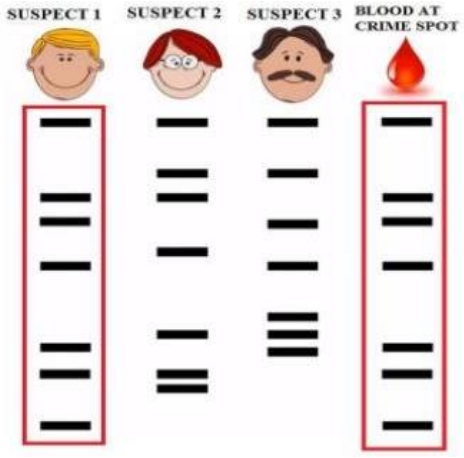
RFLP Is useful in:

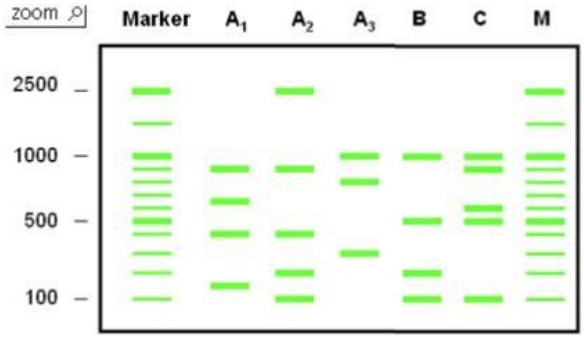
- Disease diagnosis
- Forensic investigation
- Paternity Dispute

RFLP in Disease Diagnosis



RFLP in Crime Investigation





- Assuming C is a parent of B, who is the other parent (A1, A2 or A3)?

Ans: A1

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